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THE OPERATED STOMACH

A clinical study on late morbidity and mortality rates
in patients operated on for benign gastroduodenal
disease, with special reference to the risk of
developing gastric cancer



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CONTENTS

ABBREVIATIONS	4
INTRODUCTION	5
AIM OF THE STUDY	11
I. LATE MORTALITY AFTER SURGERY FOR BENIGN GASTRODUODENAL DISEASE	12
Material and methods	13
Results	17
Discussion	19
II. DEATH FROM CANCER IN THE OPERATED STOMACH. A STATISTICAL ANALYSIS OF RISK FACTORS	21
Material and methods	22
Results	23
Discussion	28
III. CANCER IN THE OPERATED STOMACH. A CLINICAL STUDY OF 61 PATIENTS	31
Material and methods	32
Results	33
Discussion	39
IV. SCREENING FOR CANCER IN THE OPERATED STOMACH	42
Material and methods	43
Results	45
Discussion	51
V. CORRELATION BETWEEN CLINICAL SYMPTOMS AND GASTROSCOPIC AND HISTOLOGICAL FINDINGS IN PATIENTS OPERATED ON FOR BENIGN GASTRODUODENAL DISEASE	53
Material and methods	54
Gastrosocopy 1972/1973, definitions	54
Histology, definitions	55
Results	55
Discussion	61
VI. CORRELATION BETWEEN GASTROSCOPIC AND HISTOLOGICAL FINDINGS IN BIOPSIES TAKEN 12 TO 49 YEARS AFTER SURGERY FOR BENIGN GASTRODUODENAL DISEASE	64
Material and methods	65
Gastrosocopy 1978/1979, definitions	65
Results	67
Gastrosocopy findings, examples	68
Discussion	73
VII. CAN GASTROSCOPIC OR MICROSCOPIC FINDINGS IN BIOPSIES BE USED TO PREDICT THE DEVELOPMENT OF GASTRIC CANCER IN THE OPERATED STOMACH	75
Material and methods	76
Results	77
Discussion	80
GENERAL SUMMARY	85
ACKNOWLEDGEMENTS	106
REFERENCES	107

This thesis is based on the following reports:

- I. Late mortality after surgery for benign gastroduodenal disease.
Sten Eriksson, Bengt Huldt & Gustav Liedberg.
- II. Death from cancer in the operated stomach. A statistical analysis of risk factors.
Sten Eriksson & Gustav Liedberg.
- III. Cancer in the operated stomach. A clinical study of 61 patients.
Sten Eriksson, Gustav Liedberg & Eric Hammar.
- IV. Screening for cancer in the operated stomach.
Sten Eriksson, Bengt Huldt, Eric Hammar & Gustav Liedberg.
- V. Correlation between clinical symptoms and gastroscopic and histological findings in patients operated on for benign gastroduodenal disease.
Sten Eriksson, Berngt Huldt, Eric Hammar & Gustav Liedberg.
- VI. Correlations between gastroscopic and histological findings in biopsies taken 12-47 years after surgery for benign gastroduodenal disease.
Sten Eriksson, Gustav Liedberg, Eric Hammar & Bengt Huldt.
- VII. Can gastroscopic or microscopic findings in biopsies be used to predict the development of gastric cancer in the operated stomach?
Sten Eriksson, Gustav Liedberg, Eric Hammar & Bengt Huldt.

These reports will be referred to in the text by their Roman numerals.

ABBREVIATIONS

AG	Acute gastritis	55
AGC	Advanced gastric cancer	32
API	Atypia	56
CAG	Chronic atrophic gastritis	55
CHG	Chronic hyperplastic gastritis	56
CG	Chronic gastritis without atrophy	55
EGC	Early gastric cancer	32
ERG	Endoscopic reflux gastritis	54
IM	Intestinal metaplasia	56
PRG	Postoperative reflux gastritis	7

INTRODUCTION

One century has passed since Billroth (6) on January 29th, 1881, performed the first successful gastric resection, opening the era of modern gastrointestinal surgery. During this century surgical treatment for benign gastroduodenal diseases has been performed on an increasing number of patients. The type of procedures used and the indications for treatment have changed with time. Distal gastric resection and gastroduodenostomy (Billroth I) was first performed already in 1882 by Rydiger (121) but it was not until the beginning of the thirties that resections outnumbered the simple gastroenterostomy. Primbaum's report (110) on the poor results after gastroenterostomy and the coining of the phrase of "gastroenterostomy as a disease" strongly contributed to this process. When resections were performed gastrojejunostomy (Billroth II) rapidly became the most common way of reconstructing the gastrointestinal continuity. The selection of surgical procedure was seldom influenced by the type of ulcer disease until the beginning of the sixties. Earlier, gastric and duodenal ulcers were looked upon as belonging to the same peptic ulcer disease. During the last decade the number of operations performed has decreased due both to more effective medical treatment and to a decrease in the incidence of duodenal ulcer (41).

This thesis is, consequently, discussing a problem that will diminish. However, 1 % of the adult population is still estimated to have had gastric surgery performed for a benign gastroduodenal disease (55).

When studying late morbidity today, one finds that the majority of operated patients have been resected. Most of them are satisfied with the operation and consider themselves to be free of symptoms in the upper gastrointestinal tract. Nevertheless, approximately 15 % either have not been cured or complain of symptoms they did not experience before the operation (10, 143). The pattern of symptoms is uniform enough that in parallel with Primbaum's quotation "gastroenterostomy as a disease" we could as well talk about the "Billroth disease" in patients that experience postprandial epigastric fullness, pain, nausea and bile-stained vomits and who have a desire to lie down and rest after meals. However, after a thorough analysis of symptoms different syndromes have been identified.

Recurrent ulcer

Recurrent ulcer was earlier regarded as a serious complication after "curative" surgery for peptic ulcer disease. It was characterized by a high mortality rate and many therapeutical problems. The literature on recurrent ulcer is extensive indicating that follow-up studies have mainly been focused on this problem (10, 47, 67, 111, 119). Recurrence rate after a three quarter resection is reported to

be approximately 2-3 % (67). Less extensive resections cause less other side effects but increases the probability of a recurring ulcer (111, 119). The majority of ulcers in the operated stomach occur within a few years after surgery except after simple gastroenterostomy where Cleaton (18) reports a mean interval to reoperation of 17 years. The symptoms are usually those the patient experienced before surgery. Today recurrent ulcers are less problematic since they are easy to diagnose with gastroscopy (23) and easy to treat with modern effective inhibitors of gastric acid secretion (e.g. H_2 -receptor blocking agents) (77).

Early dumping

In 1913 Hertz (59) described the phenomenon of "too rapid emptying of the stomach after gastrectomy" associated with fullness, nausea, diarrhoea and tachycardia. The term dumping of the stomach's contents into the jejunum was first used by Andrews (3) in 1920 and Mix in 1922 (94). Vasomotor and cardiovascular symptoms usually predominate, and the sequence of the symptoms shows important characteristics. Within 5-10 minutes after eating the patient experiences a feeling of fullness in the epigastrium, then a characteristic flush occurs followed by pallor, sweating and a feeling of weakness. Ten to 20 minutes later the vasomotor symptoms disappear and nausea, vomiting and diarrhoea may predominate. Meurling has described and classified the syndrome in detail (89). After gastric resection, 1/3 of 504 patients reported by Harvey et al (54) experienced dumping and the symptoms persisted in 13 % during follow-up.

Afferent loop syndrome

The first reported sequel after resection consisted of nausea and bile vomits and was described as early as in 1881 by Wölfler (149). This syndrome has been called the afferent loop syndrome and occurs in an acute and a chronic form (26). The incidence of acute afferent loop syndrome is approximately 0.5 % after partial gastrectomy. It is characterized by the acute onset of severe epigastric pain with occasional vomits, characteristically without bile admixture, jaundice and hyperamylasemia. Dahlgren (26) states that it occurs in the immediate postoperative period in 30 % of the cases. The causes are internal herniation, nicking of the afferent loop, adhesions and stenosis. Dahlgren also studied a chronic form of afferent loop syndrome, consisting of a combination of postprandial fullness and colicky pain relieved by vomiting of large volumes of bile-stained liquid. It most frequently occurs after an antecolic anastomosis without enteroanastomosis and the etiology is believed to be intermittent obstruction of the afferent loop. Postprandially pressure increases in the afferent loop, causing nausea and pain. When the pressure overcomes the obstruction the duodenal contents are emptied into the gastric remnant, causing an often violent attack of vomiting followed by symptomatic relief. The ingested food

has then already passed down the efferent loop and therefore usually is not a part of the vomit. The diagnosis of chronic afferent loop syndrome is based on an analysis of symptoms, radiological and gastroscopical examinations. Further, Dahlgren suggested a provocation test with intravenous secretin and cholecystokinin in order to establish the diagnosis.

Postoperative reflux gastritis

Until the middle of the sixties all patients with bile vomits were considered to have an afferent loop syndrome. Wells & Welbourn (146) showed, however, that some patients had no evidence of mechanical obstruction of the afferent loop and they also observed the same symptoms among patients having a Billroth I-resection. Toye & Alexander-Williams (141) showed in 1965 that external drainage of the afferent loop contents in a Billroth II-resected patient with severe symptoms of postprandial nausea and bile vomits resulted in complete relief of symptoms. Infusion of saline in the gastric remnant could not provoke symptoms whereas the drained duodenal contents could. They concluded that reflux of duodenal contents into the gastric remnant were responsible for postprandial nausea, pain and bilious vomits. van Heerden et al (144) suggested the term postoperative alkaline reflux gastritis. This term has been considered misleading since it is not probable that the alkalinity as such causes the condition. Postoperative reflux gastritis has later been widely used. van Heerden et al (145) have categorized the syndrome as a combination of pain, bilious vomits, anaemia, gastric hyposecretion and gastroscopic evidence of gastritis.

Afferent loop syndrome and postoperative reflux gastritis may coincide. An analysis of the character of symptoms has been suggested to be helpful in the differential diagnosis (109, 127). Pain in afferent loop syndrome is more bursting, cramping, crushing, and colicky in character, occurring only postprandially and being promptly relieved by a projectile vomit containing no food. The pain in postoperative reflux gastritis is more continuous of a burning and aching character being aggravated by meals and not completely relieved by vomiting. Vomits are less projectile and often contain residual food. Still it may be difficult in an individual patient to differentiate the two syndromes on the basis of the character of symptoms involved. The endoscopic picture has then been suggested as a discriminator. van Heerden et al (145) consider the findings of adherent mucous, oedema, mucosal friability and erosions on the gastric aspect of the anastomosis to be associated with the syndrome of reflux gastritis. The endoscopic picture has been studied by Keighley et al (71) in 28 cases, with and without symptoms. They found more hyperemia in patients with symptoms. The criteria for endoscopic reflux gastritis have not been established and the correlation with individual symptoms or histological findings has not been studied in an unselected population of patients.

Objective tests to verify the syndrome of reflux gastritis has been suggested (1, 140), e.g. Technetium-labelled HIDA, scanning over the gastric area and infusion of the patient's own duodenal contents into the gastric remnant.

Other less common syndromes have been described, e.g. late dumping, the efferent loop syndrome, postgastrectomy malabsorption and anaemia, and postgastrectomy bone disease. For an excellent review on different postgastrectomy syndromes the reader is referred to "Postgastrectomy and Postvagotomy Syndromes" edited by Becker and Caspary (109).

Late mortality after gastric surgery

With a surgical mortality that in elective cases is less than 1 % and with 85 % overall good or excellent results during follow-up (10, 47), surgical treatment might be considered satisfactory. Still one out of seven patients either is not cured or contracts another chronic disease described earlier as belonging to one or more of the different postgastrectomy syndromes. In both situations severe symptoms may sometimes be treated by a new surgical intervention although at the cost of a higher postoperative mortality. Nevertheless, as peptic ulcer is a chronic and in many cases disabling disease, the results from surgical treatment could be considered satisfactory provided long-term survival was not affected by the surgical procedure. Some reports, however, suggest that premature death is common. Krause (78) followed 361 patients 23-50 years after a Billroth II-resection and found an increased overall mortality during follow-up. The same results were reported by Ross et al (118) who found the shortening of life expectancy after surgery to be nine years.

If this were true for all operated patients and could be shown to be due to the operation as such and not to the ulcer disease or selection of patients the indications for surgery must be revised and preventive measurements taken during follow-up.

Smoking-associated diseases, e.g. lung cancer, and chronic bronchitis were regarded as the main cause of premature death in Ross' series. Of the patients, 83 % were cigarette smokers at the operation and few ceased to smoke afterwards. Bonnevie (8) has reported more deaths from the same diseases among peptic ulcer patients. Thus, the number of deaths from these smoking-associated diseases may not be altered by the gastric operation per se.

An increased incidence of suicide has also been reported. The average incidence seems to be 3-4 % (78, 118) of all deaths during an interval of up to 20-30 years after surgery, but Knop & Fisher (74) have reported a number as high as 13.7 %. Viskum (147) has investigated attempted suicides and suicides among peptic ulcer patients and found that both operated and not operated patients attempted and committed suicide significantly more often than expected, but found no differences between medically and surgically treated patients. It

therefore seems appropriate to assume that disposition to suicide is associated with the peptic ulcer disease.

Gastric cancer

Since Balfour's (4) first description of a cancer in the gastric remnant after surgery for a benign condition in 1922 this clinical entity has become widely recognized. The definition of the disease (28), often recognized as "stump cancer", is that at least five years must have elapsed since the primary operation in order to exclude the possibility of a previously undetected cancer. Different opinions exist as to whether or not the operated stomach should be recognized as a precancerous condition, e.g. associated with a higher risk of developing cancer compared to the non-operated stomach (27, 57, 95, 105, 106).

Kühlmayer & Rokitansky (79) and Hilbe et al (60) performed autopsy studies showing cancer in the operated stomach to be twice as common as in matched controls, but Kivilaakso et al (73) could not verify their findings. The most commonly cited work is that of Stahlsberg & Taksdal from 1971 (134) . They reported among 17 000 autopsies 630 verified gastric cancers. Significantly more patients with gastric cancer had had a gastric operation performed more than five years prior to death than patients in a matched control group. They also showed that the ratio between observed and expected number of gastric cancer deaths increased with increasing length of the interval between surgery and death.

In clinical follow-up studies different results have, again, been published. Krause (78) in 1954 performed a study 23-50 years after surgery. He was able to trace 361 out of 385 patients and found the observed risk of dying from gastric cancer twice the expected. In other similarly performed follow-up studies this result could not be verified (86, 118). One risk factor suggested above is the length of time after surgery. The magnitude of the risk involved has recently been studied by Hellers et al (55). They showed that the risk increased steadily reaching 25 times the expected 35 years or more after surgery.

Other risk factors have been considered, e.g. sex, age at surgery, type of operation performed and type of peptic ulcer disease. The relative importance of these risk factors is a matter of controversy. Domellöf et al (35) found that only males had an increased risk of developing stump cancer. Most reported cases have been Billroth II-resected (105) but perhaps this finding only reflects the fact that gastroduodenostomy was seldom used 20-30 years ago. Considerable discrepancies in opinions exist whether gastric or duodenal ulcer diseases are associated with increased, normal or decreased risks (17, 48, 56, 60, 101, 107). In the above mentioned autopsy studies no differences were found in this respect. Hilsingen & Hillestad (56) performed a clinical follow-up study and reported that duodenal ulcer

surgery was associated with an unaltered risk whereas after operations performed for gastric ulcer three times as many patients as expected developed cancer. Age at surgery as a risk factor has only been investigated by Brollo et al (11). In an autopsy study they found an increased risk of developing cancer if the patients were younger than 45 years at the time of surgery.

The overall risk of dying of gastric cancer after an operation for benign gastroduodenal disease has been reported to be as high as 10 % (60) but the average reported figure is 3 % (46). Obviously, several risk factors must be considered and the distribution of these, in different patient series may explain some of the differences found.

In follow-up studies with gastroscopy and biopsy, e.g. those performed by Domellöf et al (32, 33) and Schrupf et al (125) considerable numbers of early gastric cancer were detected. The prognosis for patients with advanced cancer is reported to be miserable and for patients with early cancer favourable (42, 108, 150). The possibility of lowering mortality rates in gastric cancer by screening operated patients with gastroscopy and biopsy has initiated screening procedures in many centers. However, there are no reports on the influence of the surgical treatment of early gastric cancer on gastric cancer mortality rate. Many have hesitated to initiate screening due to the large number of individuals that have been operated on for benign gastroduodenal disease. So far the only selection criterion established is the length of the time interval after surgery, where 15 years has been recommended as a starting point for screening (33). More detailed criteria might increase the yield to an extent that screening could be performed on high risk patients with available gastroscopic resources.

After screening a population another problem appears. Which is the optimal interval to the next screening and could the information obtained from one examination be used to identify high risk patients?

Microscopical changes in the gastric mucosa such as chronic atrophic gastritis, intestinal metaplasia and atypia or dysplasia are considered precancerous lesions (97). These changes are often seen in biopsies from the operated stomach (33, 123, 125). From follow-up studies on non-operated patients with chronic atrophic gastritis, Siurala et al (131) and Walker et al (142) concluded that chronic atrophic gastritis could be regarded as a precancerous lesion. Studies on intestinal metaplasia irrespective of other findings have not been performed but intestinal metaplasia is often seen in the mucosa adjacent to gastric cancer (96, 115). The importance of this finding as a possible cancer precursor is not known. The degree of dysplasia is regarded by Morson et al (97) to be a sensitive indicator of the risk of developing gastric cancer but no results have been published concerning the magnitude of that risk.

Apparently a number of important questions concerning the risk for the ulcer operated patient of dying of gastric cancer and the histological changes preceding the development of cancer remain to be answered.

The aim of the present investigation has been to study and discuss the following questions:

1. Is the overall long-term mortality rate, in patients operated on for benign gastroduodenal disease increased?
2. Is the mortality pattern changed in these patients?
3. Is there an increased risk of dying of gastric cancer after surgery for benign gastroduodenal disease?
4. What is the importance of some clinical parameters, e.g. sex, age at operation, indication for surgery, type of operation performed and time after surgery, for the risk of later death in gastric cancer?
5. Is surgical treatment of gastric cancer in the operated stomach worthwhile?
6. What can be gained by screening operated patients with gastroscopy and biopsy?
7. Which selection criteria could be recommended to increase the detection of gastric cancer from screening?
8. Is there any correlation between clinical symptoms, endoscopical findings and histological changes in patients with previous gastric surgery?
9. Are there any microscopic or endoscopic criteria which can be used to predict the development of cancer in the operated stomach?
10. Are chronic atrophic gastritis, intestinal metaplasia and atypia precancerous lesions in the operated stomach and is the severity correlated with the risk of developing gastric?

I. LATE MORTALITY AFTER SURGERY FOR BENIGN GASTRODUODENAL DISEASE

SUMMARY

At the Department of Surgery in Lund, 1 575 patients were operated on for benign gastroduodenal disease with gastric resection or gastroenterostomy during 1930 to 1960. After discharge from the hospital, 172 patients could not be traced leaving 1 403 to be followed. During follow-up until October 1st, 1979, 763 patients had died. The main cause of death according to the death certificate was registered and the observed number of deaths in different diagnoses were related to the expected numbers computed from Swedish death statistics.

A significant increase in the observed number of deaths were found for benign and malignant pulmonary diseases, general arteriosclerosis and suicide. The observed number of deaths in gastric cancer did not differ from the expected. The overall mortality rate during follow-up was increased only if postoperative deaths were included. However, in the subgroup of patients operated on before the age of 40, an increased risk of premature death was found.

Follow-up studies after surgery for benign gastroduodenal disease have mostly focused on the recurrence of peptic ulcer and to a lesser extent on postgastrectomy syndromes such as dumping and malnutrition (10, 47, 119, 143). Long-term survival and mortality pattern among operated patients have infrequently been investigated (132).

Krause (78) reported an increased overall mortality 23-50 years after Billroth II-resection, mainly due to an excess mortality in pulmonary tuberculosis, gastric cancer and suicide. Other studies have confirmed the increased risk of premature death after peptic ulcer surgery. Ross et al (118) showed a shortening of life expectancy of 9 years mainly due to diseases associated with smoking.

The aims of the present study were to investigate whether an increased overall mortality after surgery for benign gastroduodenal diseases could be found in a series of patients operated on in Lund, Sweden, and to relate the reported mortality rates in different diagnoses or group of diagnoses to those expected according to the official Swedish death statistics. Our main interest was to examine the mortality due to gastric cancer since opinions differ as to whether or not cancer in the operated stomach is a cause of excess mortality.

MATERIAL AND METHODS

1. The series

All patients operated on for benign gastroduodenal disease with gastric resection or gastroenterostomy, with or without vagotomy, at the Department of Surgery, Lund, Sweden, from 1930 through 1960 were identified from the hospital files. For each patient, the following data were recorded: date of birth and surgery, sex, indication for and type of operation performed. For those who died during the follow-up period, the main cause of death given by the death certificate was recorded according to WHO nomenclature. Patients who died from gastric cancer within five years after the operation were excluded since it was assumed that these patients might have had cancer at the time of surgery. A total of 28 deaths from gastric cancer was found. The original histological specimens could be checked in 20 patients. In three a gastric cancer was already present at the primary operation and thus these three were excluded. One patient was excluded as he actually died from colonic cancer. Thus, of 24 remaining patients with gastric cancer as the registered cause of death, 16 had a verified and eight an assumed benign condition at the time of operation. For patients operated on more than once the date of the first operation was recorded while the last operation performed was recorded as the type of surgical procedure. Patients with combined gastric and duodenal ulcers were registered in the group of miscellaneous diagnoses. All recorded data were stored and analysed using an Univac 1100/80 computer.

2. Sex and age at primary surgery

The male to female ratio was 4.5:1. Males were on the average 3-4 years younger when operated on for both duodenal and for gastric ulcers. The male to female ratio for duodenal ulcer patients was 5.6:1 and for gastric ulcer 3.6:1. The mean age ($\pm$ SD) for 811 men with a duodenal ulcer was 45.2 ± 12.6 and for 146 women 48.1 ± 12.3 years. The mean age for 381 men with a gastric ulcer was 52.9 ± 10.8 and for 107 women 56.2 ± 11.7 . The number of patients in different age groups is shown in Fig 1.

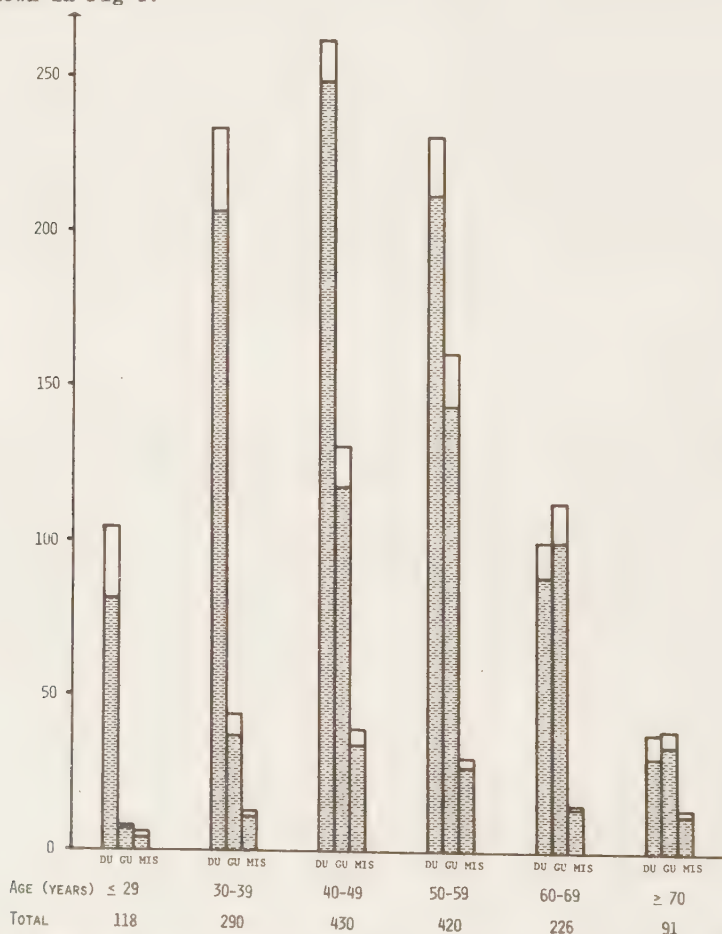


Fig 1. Number of patients operated on for duodenal ulcer (DU), gastric ulcer (GU) and miscellaneous diagnosis (MIS) in different age groups. Unshaded parts of columns denote patients who could not be traced.

3. Surgical procedures and indications for surgery

Gastroenterostomy was the most common surgical procedure for benign gastroduodenal disease in the beginning of the series (Table I).

TABLE I
SURGICAL PROCEDURES

Type of operation	Total number	Number of operations and column percentage						
		Year						
		1930-34	1935-39	1940-44	1945-49	1950-54	1955-59	1960
Billroth I	205	29	21	4	8	17	91	35
	13%	25%	18%	3%	3%	4%	21%	47%
Billroth II	1 203	32	60	94	221	433	325	38
	76%	27%	52%	80%	86%	93%	76%	51%
Gastroenterostomy	155	56	34	17	22	13	11	2
	10%	48%	29%	15%	9%	3%	3%	2%
Other types of resection	12	-	1	2	5	2	2	-
	1%	-	1%	2%	2%	-	-	-
Total number	1 575	117	116	117	256	465	429	75

The number of operations per year gradually increased with time and the Billroth II-type of resection grew more popular. In the middle of the fifties between 90 and 100 operations were performed yearly. The standard procedure was a 3/4 resection with a short afferent limb and a retrocolic anastomosis without enteroanastomosis. A change to Billroth I-resection is apparent during the last years of the series. The ratio between duodenal and gastric ulcers remained at 2:1 during the period studied (Table II).

TABLE II
INDICATIONS FOR SURGERY

Indications	Total number	Number of operations and column percentage						
		Year						
		1930-34	1935-39	1940-44	1945-49	1950-54	1955-59	1960
Duodenal ulcer	965	65	79	67	154	298	263	39
	61%	56%	68%	57%	60%	64%	61%	52%
Pyloric ulcer	58	14	3	6	15	16	3	1
	4%	12%	3%	5%	6%	4%	1%	2%
Gastric ulcer	493	38	28	38	65	140	153	31
	31%	32%	24%	33%	25%	30%	36%	41%
Miscellaneous	59	-	6	6	22	11	10	4
	4%	-	5%	5%	9%	2%	2%	5%
Total number	1 575	117	116	117	256	465	429	75

4. Postoperative mortality

Postoperative mortality is defined as death occurring during the hospital stay. All emergency operations are included in the series. There was a steady decrease in postoperative mortality from 9 % in the beginning of the period to 2.8 at the end (Table III). Mean age at operation for was 55 years succumbing patients.

TABLE III

POSTOPERATIVE MORTALITY		1930-39			1940-49			1950-60		
Type of operation	Total deaths	Deaths	No. of operations	%	Deaths	No. of operations	%	Deaths	No. of operations	%
Billroth I	11	3	50	6	0	12	-	8	143	5.6
Billroth II	38	8	92	8.7	12	315	3.8	18	796	2.3
Gastroenterostomy	14	10	91	11	3	39	7.7	1	26	3.8
Other types of resection	-	-	1	-	-	7	-	-	4	-
Total number	63	21	233	9.0	15	373	4.0	27	969	2.8

5. Follow-up

Out of 1 575 patients 172 could not be traced leaving 1 403 (1 157 males and 246 females) to be followed. Those who emigrated or were lost to follow-up in other ways are registered as "withdrawn alive", during the year they were lost. The follow-up was terminated on October 1st 1979. At that time 763 (54 %) had died, 619 (44 %) were still alive and 21 (1.5 %) had been withdrawn alive. The total number of observation years was 28 926 (Table IV).

TABLE IV

FOLLOW-UP	Number of patients	Number of observation years	Observation years per patient, mean	Dead Oct 1st 1979	Withdrawn alive	Alive Oct 1st 1979
Male	1 157	24 132	20.9	614 (53 %)	16 (1.4 %)	527 (46 %)
Female	246	4 794	19.5	149 (60 %)	15 (2.0 %)	92 (37 %)
Total	1 403	28 926	20.6	763 (54 %)	21 (1.5 %)	619 (44 %)

6. Statistical methods

The patient's risk of dying from a specific disease has been computed from the figures in the publication "Causes of death" by the National Central Bureau of Statistics in Sweden for each year a patient has been observed. The risk was adjusted for age, in five-year intervals, and sex, but not for region in Sweden. To compensate for changes in diagnostic skill and incidence of disease, the risks up to 1957 have been computed on the basis of the 1957 year publication, between 1958 and 1967 from the 1967 year publication, and from 1968, from the 1977 year publication of Causes of Death. Death statistics prior to 1955 could not be used to study all the individual diagnoses. Eleven different diagnoses or diagnostic groups have been studied as well as the total mortality.

The annually expected number of deaths during the study has been computed on the basis of the number of patients observed during that year. The expected number of deaths during the follow-up period is the sum of the expected numbers for each year. When testing the significance of differences between observed and expected numbers it is assumed that observed number of deaths has a Poisson distribution.

7. Causes of death studied

The initial purpose of the study was to investigate the risk of dying of gastric cancer (WHO 151). Colorectal cancer (WHO 153-154) was chosen as an other gastrointestinal cancer with no expected relation to ulcer disease. Most peptic ulcer patients smoke. We therefore studied lung cancer (WHO 162) and bronchopneumonia (WHO 480-486), ischemic heart diseases (WHO 410-414), cerebrovascular diseases (WHO 430-438), and general arteriosclerosis (WHO 440-448).

Benign oesophago-gastro-duodenal diseases (WHO 530-537) were chosen in order to give an idea of the long-term results of the surgically treated disease. From earlier studies we know that operated patients commit suicide (WHO E 950-959) more often than expected. Suicide is often associated with alcoholism, and we have therefore studied benign liver and pancreatic diseases (WHO 570-577).

RESULTS

In Table V the observed and expected numbers of deaths for men and women are given for all diagnoses studied as well as the total mortality.

TABLE V

NUMBERS OF EXPECTED AND OBSERVED DEATHS DURING FOLLOW-UP

Main cause of death WHO code	Male			Female			Total		
	Expected deaths	Observed deaths	Sign.	Expected deaths	Observed deaths	Sign.	Expected deaths	Observed deaths	Sign.
151	17.9	20	NS	2.8	4	NS	20.7	24	NS
153	9.3	12	NS	2.2	1	NS	11.4	13	NS
154	5.7	3	NS	0.8	0	NS	6.5	3	NS
162	17.1	38	***	0.8	3	*	17.8	41	***
410-414	206.4	161	**	35.9	42	NS	242.3	203	*
430-438	57.4	48	NS	17.8	11	NS	75.2	59	NS
440-448	16.7	32	**	4.6	9	*	21.3	41	**
480-486	20.4	51	***	5.4	10	*	25.8	61	***
530-537	6.8	8	NS	0.8	2	NS	7.7	10	NS
570-577	8.7	14	NS	1.9	0	NS	10.6	14	NS
950-959	11.4	35	***	0.7	3	**	12.1	38	***
Total	563.8	612	*	114.6	151	***	678.3	763	**

NS = not significant, * = $0.01 < p < 0.05$, ** = $0.001 < p < 0.01$, *** = $p < 0.001$.

A total of 763 deaths were registered during the follow-up and of these 63 occurred postoperatively. The expected number was 678 which is not significantly different from the observed if postoperative mortality is excluded. An increased risk of premature death can, however, be noticed in patients operated on under the age of 40 (observed 76, expected 55.2, $p < 0.01$). The observed number of gastric cancer deaths did not differ from the expected. For a further detailed analysis see II. The observed number of colorectal cancer deaths did not differ from the expected.

We observed 41 lung cancer deaths, a significant ($p < 0.001$) increase compared to the expected (17.8). The risk is more pronounced for men than for women. Patients with gastric ulcer had a higher risk (observed 19/expected 5.9) than those with duodenal ulcer (observed 20/expected 11.3). Males operated on for duodenal ulcer before the age of 40 and males operated on for gastric ulcer after the age of 60 were found to be special risk groups. A significant ($p < 0.001$) increase in the risk of dying of bronchopneumonia (observed 61/expected 25.8) was found. No special risk groups could be identified when the age at surgery or the type of ulcer disease was considered.

Three different groups of cardiovascular diseases were studied. We observed less (203) deaths in acute and chronic ischemic heart diseases than expected (242). The difference is significant ($p < 0.05$) but is only valid for duodenal ulcer and not for gastric ulcer patients. The observed death rate in cerebrovascular diseases did not differ from the expected. Forty-one deaths in general arteriosclerosis were observed and 21.3 expected ($p < 0.01$). No differences were noted when patients were grouped according to age at surgery or type of ulcer disease.

The observed number of deaths in benign oesophagogastroduodenal disease (10) did not differ from the expected (7.7). The numbers are too small to permit any definite conclusions to be drawn but suggest that after surgical treatment for ulcer disease the risk of dying of benign oesophagogastroduodenal diseases is not increased.

Fourteen deaths were observed in benign liver, gallbladder and pancreatic diseases and the number did not differ from the expected (10.6). During the follow-up period 38 patients died by suicide against an expected 12.1. The difference is significant ($p < 0.001$). Men operated on for duodenal ulcer after the age of 60 seem to form a special risk group (observed 6/expected 0.6) as well as patients operated on for gastric ulcer before the age of 40 (observed 3/expected 0.4).

DISCUSSION

The surgical technique of treating peptic ulcer disease reflects an influence from German surgeons during the thirties. Even if Primbaum (110) had stated, as early as 1923, that resection gave better results than gastroenterostomy alone and that gastroenterostomy should be looked upon as a disease it took time before "das Grosse Magenresektion" became the most common operation for treating peptic ulcer. The influence of Anglo-Saxon surgeons after World War II gradually changed the overall resection pattern to the allegedly more "physiological" Billroth I-resection or to vagotomy with pyloroplasty (not included in this study).

In this series the male to female ratio was approximately the same as reported by others but strikingly more patients with gastric ulcers have been operated in Lund. A ratio between gastric and duodenal ulcers of 1:2 is similar to what Knutsen & Selvaag (75) found as the incidence in the general population in Norway 1973. The ratio reported in other surgical series is usually 1:4-5 (9, 47, 143).

In a longitudinal study of elderly men in Gothenburg, Sweden, Mellström & Rundgren (90) reported that 95 % of resected patients were smokers or ex-smokers compared to 78 % of non-operated males of the same age. Similar figures for smoking habits were given by Ross et al (118). Premature death in both benign and malignant pulmonary diseases has been reported in several studies on late mortality after peptic ulcer surgery (31, 78, 118). In this study we could verify earlier reports. In addition it seems that males operated early in life were exposed to the highest risk of lung cancer death.

Ross et al (118) found that the number of deaths caused by ischemic heart diseases during follow-up was not different from that expected. In our series we actually found less deaths than expected. This could be due to the fact that patients with overt cardiovascular disease were excluded in the selection of patients for elective surgical treatment of peptic ulcer. In the above-mentioned study from Gothenburg the

prevalence of arterial hypertension in resected patients was lower than in non-resected. If the finding is valid also for patients in our series it may explain why the number of deaths in cerebrovascular diseases were within the expected as on the other hand more deaths than expected were found of general arteriosclerosis.

Since Krause first reported an increased risk for premature death by suicide several follow-up studies have shown similar results (118, 147). Knop & Fischer (74) estimated that during a 21-29 year follow-up of 1 000 patients 13.7 % of all deaths were suicides. Fifty per cent of those who committed suicide were abusing alcohol. In our series suicide was the cause of death in 5.4 %. Furthermore, we could not detect an increased risk of dying of benign liver or pancreatic diseases as reported e.g. by Ross et al. This discrepancy might be explained by differences between the populations studied. Knop & Fischer's series was collected from the central part of Copenhagen while ours was mainly collected from rural areas. Viskum (147) studied attempted and committed suicides in 2 619 patients with a peptic ulcer disease. The number of patients committing and attempting suicide exceeded the expected but no difference was found between operated and non-operated patients indicating that the increased risk may be related to the ulcer disease and not to the operation.

An increased overall mortality rate has been found in several follow-up studies (17, 31, 78, 132). Ross' series, that only includes males, found a shortening of life expectancy by 9 years regardless of the age at surgery, and comments that these patients are bad risks indeed in life insurance terms. We could verify these results only for males operated before the age of 40.

The main medical problem for patients operated on for benign gastro-duodenal disease seems to be their smoking habits. Reduced mortality is probabyl best achieved by intensified information, especially to patients operated at a young age.

II. DEATH FROM CANCER IN THE OPERATED STOMACH. A STATISTICAL ANALYSIS OF RISK FACTORS

SUMMARY

In a series of 1 403 patients operated on for benign gastroduodenal disease and followed for 19-49 years, 24 died from gastric cancer. This number of deaths does not differ significantly from the expected 20.7. However, an increased gastric cancer death rate was found in the subgroup of patients operated on for gastric ulcer while no influence could be ascribed to sex or to the type of operation performed. The risk of dying from gastric cancer increased exponentially with time after the operation. Life table analysis showed that gastric ulcer patients died in gastric cancer after a significantly shorter time interval than duodenal ulcer patients. However, differences in mortality rates were no longer apparent after more than 40 years follow-up.

The most important risk factor seemed to be the patients' age at surgery. Patients operated on under the age of 40 ran a four-fold increased risk of dying of gastric cancer. In fact, an inverse relationship was found between the quotient of gastric cancer deaths and all deaths and the age at operation, while theoretically, a direct relationship was expected. The relative risk of dying in gastric cancer was increased in patients operated on under the age of 51 and decreased in patients operated on at a higher age.

The proportion of gastric cancer deaths to all deaths in different age groups did not seem to be the same among the operated patients as in the general population, suggesting that cancer in the operated stomach is not an age specific disease to the same extent as gastric cancer in the general population.

In a retrospective study on patients operated on for benign gastroduodenal disease, and followed for a period of 19-49 years we found the number of gastric cancer deaths within the range of the expected (I). Since an increased risk of developing gastric cancer has been reported by several authors (17, 35, 56, 60, 78) but denied by others (14, 73, 86, 118) it seemed to be of interest to perform a detailed analysis of possible risk factors. In the present report, the following parameters have been studied: sex, age at operation, type of operation performed, the indication for surgery and the time interval between operation and death of gastric cancer. Further, since it is well known, that the mortality rate of gastric stump cancer increases with time after surgery and consequently with increasing age of the patient, it has been suggested that cancer in the operated stomach is an age specific disease not different from gastric cancer in the general population (36, 57, 138). This assumption has been tested by studying the relative gastric cancer mortality in different age groups.

MATERIAL AND METHODS

1. The series

The patient series has been described in detail in I. In short, 1 403 patients operated on for benign gastroduodenal disease were followed for 19-49 years, during which time 24 died from gastric cancer according to their death certificates.

2. Statistics

The expected numbers of gastric cancer deaths in the whole series and in the different subgroups were estimated as described in Chapter I. When testing differences between observed and expected number of deaths it is assumed that observed number of deaths has a Poisson distribution.

Linear regressions were calculated using the least squares method and the correlation coefficient was calculated according to Spearman.

The life table method of Kaplan & Mayer (69) was used to illustrate the cumulative probability of specifically surviving gastric cancer (i.e., not dying of gastric cancer, other deaths were regarded as withdrawals), at different time periods after surgery. The standard deviation (SD) was estimated by Greenwoods' approximation and the difference between the life tables of two groups analyzed by the method described by Lee & Desu (40, 85).

When studying the importance of age at operation for the later death of gastric cancer, a modification of the double reciprocal plot, previously described by Liedberg et al (87) was used. Using as an analogy the dose-response relationship, the age has been regarded as

the dose and the risk regarded as the response. The inverted value of the quotient between gastric cancer deaths and all deaths was plotted against the inverted value of age in years at surgery for different age groups. The equation for the straight line best fitting the plotted values could be calculated. Thus, a simple mathematical expression for the correlation between the age at surgery and the relative risk of dying from gastric cancer could be given.

RESULTS

1. Sex, type of operation and indication for surgery

When the series was divided in different groups by the sex of the patient and the type of operation or peptic ulcer disease, no single group with significantly increased gastric cancer mortality could be identified. However, when all gastric ulcer patients, regardless of sex, were studied the observed number of gastric cancer deaths (14) was found to be significantly higher than the expected (8) ($p < 0.05$) (Table I).

TABLE I

INFLUENCES OF OPERATION PERFORMED OR TYPE OF ULCER DISEASE ON THE OBSERVED NUMBER OF DEATHS IN GASTRIC CANCER IN RELATION TO THE EXPECTED. NS = NOT SIGNIFICANT.

Operation performed	Male					Female					Total				
	No. of patients	Observed no. of years	Expected no. of deaths	Observed no. of deaths	Difference	No. of patients	Observed no. of years	Expected no. of deaths	Observed no. of deaths	Difference	No. of patients	Observed no. of years	Expected no. of deaths	Observed no. of deaths	Difference
B I	115	2357	1.9	2	NS	63	1207	0.6	1	NS	178	3564	2.6	3	NS
B II	943	19975	13.1	13	NS	143	3069	1.5	2	NS	1086	23044	14.5	15	NS
Gastro-entero-stomy	89	1602	2.7	5	NS	38	468	0.7	1	NS	127	2070	3.4	6	NS
Type of peptic ulcer disease	Male					Female					Total				
	No. of patients	Observed no. of years	Expected no. of deaths	Observed no. of deaths	Difference	No. of patients	Observed no. of years	Expected no. of deaths	Observed no. of deaths	Difference	No. of patients	Observed no. of years	Expected no. of deaths	Observed no. of deaths	Difference
DU	771	16730	10.5	8	NS	139	2796	1.4	1	NS	910	19526	11.9	9	NS
GU	343	6557	6.7	11	NS	94	1728	1.3	3	NS	437	8285	8.0	14	$p < 0.05$

2. Time interval between surgery and death in gastric cancer

The estimated risk of dying in gastric cancer increased with time after surgery, and reached 7.6 % during the five-year period 40-44 years postoperatively (Table II).

Table II. The risk of dying of gastric cancer during different 5-year intervals after surgery.

Interval	Patients exposed to risk	Terminal events	Risk	2SD
0- 4	1311.5	0	-	-
5- 9	1238	0	-	-
10-14	1134	3	0.0026	0.0030
15-19	960.5	5	0.0052	0.0046
20-24	678.5	8	0.0018	0.0083
25-29	365	3	0.0084	0.0097
30-34	145	2	0.0138	0.0194
35-39	60.5	1	0.0165	0.0328
40-44	26.5	2	0.0755	0.1026

Assuming that the risk of dying of gastric cancer (Q) increased exponentially with time, $\ln Q$ was plotted against time for each five-year period (Fig 1).

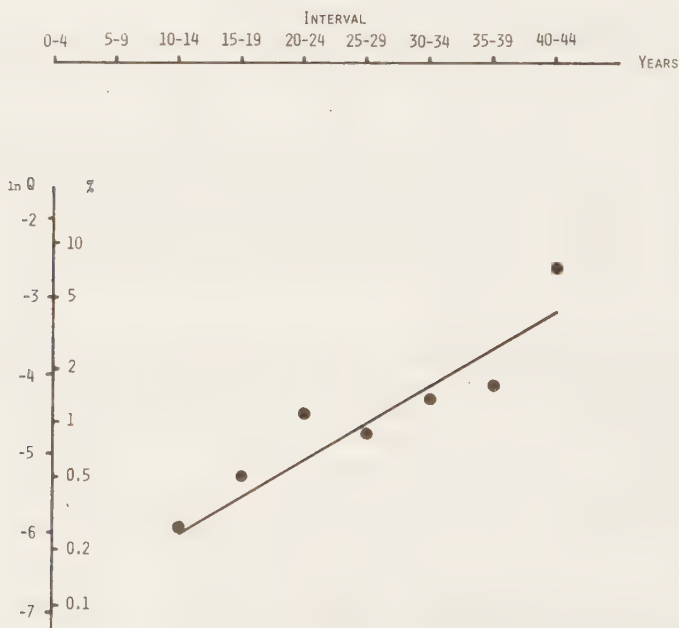


Fig 1. Risk of dying (Q) from gastric cancer during successive 5-year intervals after surgery.

A straight line with equation $\ln Q = -6.49 + 0.0678 \cdot T$ could be fitted to the observed data where T is the time in years after surgery, the correlation coefficient was 0.933 and the SD of the regression coefficient 0.017.

Using the Kaplan-Mayer plot, the cumulative probability of not dying of gastric cancer at various times after surgery is shown in Fig 2.

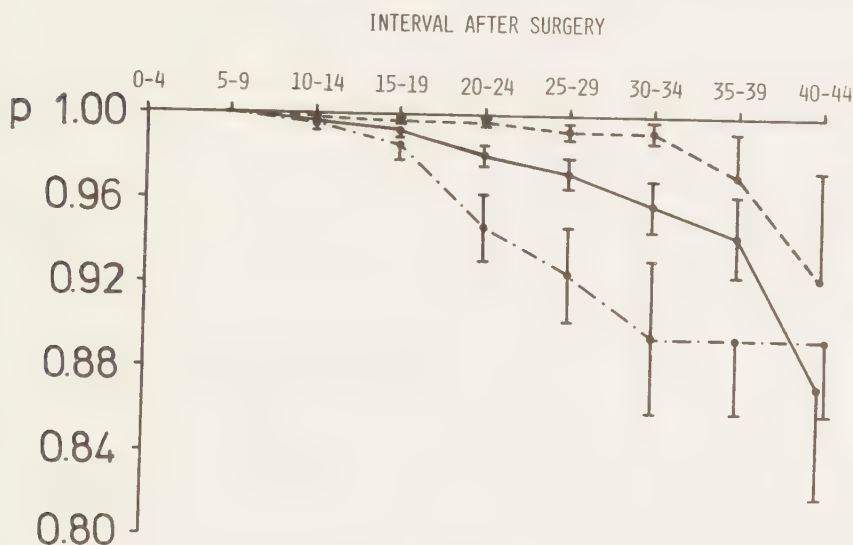


Fig 2. Actuarial cumulative probability of not dying from gastric cancer (P) for the whole series (●—●) and for patients operated on for duodenal (●—●—●) or gastric ulcer (●—●—●) separately, during the successive 5-year intervals after surgery. Bars denote ± 2 SD.

The cumulative cancer survival curve is given for the whole series as well as for the patients operated on for duodenal ulcer or gastric ulcer. The risk of dying from gastric cancer has already increased at 15 years after surgery for gastric ulcer but not until 35 years after duodenal ulcer surgery. The difference between the two curves is statistically significant ($p < 0.001$). It seems that the difference between gastric cancer mortality for gastric and duodenal ulcer patients might be less evident or even disappear if the observation time is extended to 40 years.

3. Age at operation

If the series is divided in four groups according to the age of the patient at the operation (up to and including 39, 40-49, 50-59, or 60 years and above) significantly more deaths than expected were found in the age group up to and including 39 years. No significantly increased mortality was found in patients operated on above 40 years of age (Fig 3).

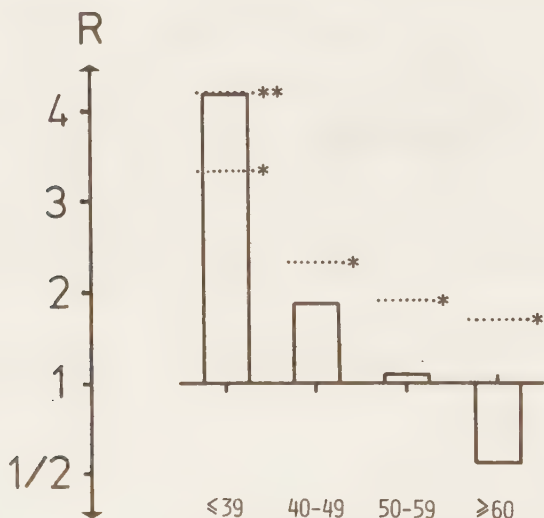


Fig 3. The ratio (R) between observed and expected number of gastric cancer deaths in operated patients, divided into groups according to age at surgery. * gives the significance levels of $p < 0.05$ and ** $p < 0.01$.

The relative risk of dying of gastric cancer (q) is defined as the quotient between cancer deaths and all deaths in a given population. If a double reciprocal plot is constructed, where $1/q$ is plotted against $1/t$ (t = mean age in years at surgery for a given group) a line can be fitted to the equation $1/q = 99.4 - 2\,892 \cdot 1/t$. If a similar plot is made for the quotient between the expected number of gastric cancer deaths and all observed deaths a line with the equation $1/q = 10.1 + 1\,414 \cdot 1/t$ is obtained (Fig 4). The intercept between the two lines indicates the age where the expected relative mortality equals the observed and can be estimated at 51 years. Thus, if an operation is performed below that age, the relative risk of later deaths from gastric cancer is increased, while after that age the risk decreases in comparison with the expected risk for the general population.

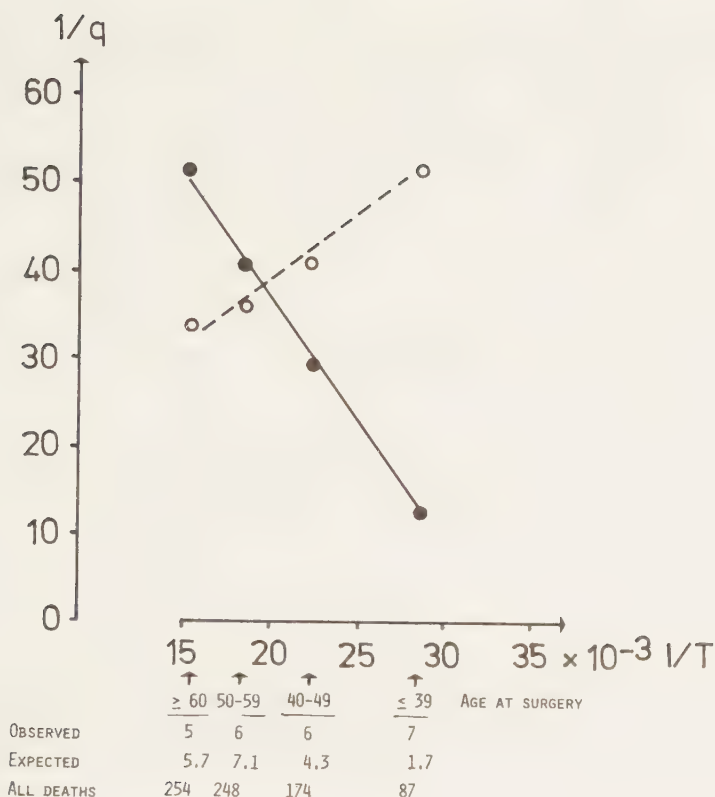


Fig 4. Double reciprocal plot of $1/q$ against $1/t$, where q is the quotient between the observed (●—●) or expected (○---○) numbers of gastric cancer deaths and all deaths in patients grouped according to age (t) at surgery.

4. Age specific relative gastric cancer mortality

The age specific relative risk of dying from gastric cancer is shown in Fig 5. In the normal population, the relative gastric cancer mortality (calculated from causes of deaths in Sweden 1977) is low in young age groups, where gastric cancer is rare, and in the old groups where other death causes are more common. The relative mortality is highest at an age between 60 and 69 years, where approximately one death in 40 is caused by gastric cancer. No such age dependent change in relative gastric cancer mortality is evident for the operated patients.

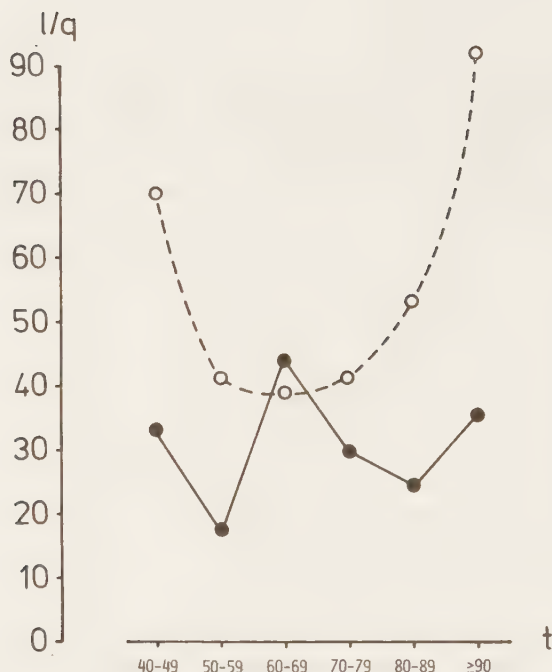


Fig 5. Age specific relative risk of dying of gastric cancer. l/q against t where q is the quotient between gastric cancer deaths and t is the age at death for the patients in the series (●—●) and for the general population (○---○), respectively.

DISCUSSION

The results of the present investigation seem to explain several of the discrepancies between previous reports on cancer in the operated stomach. We have found the risk of later death from gastric cancer after ulcer surgery to be dependent upon several factors, the most important being the age at operation, the time interval after operation and the indications for surgery. Since low age at surgery is a strong risk factor the proportion of patients operated on under the age of 40 will greatly influence the gastric cancer mortality rate in a given series of patients. In the series of Helsingen & Hillestad (56) as well as in that of Krause (78) approximately one half of the patients were operated on before the age of 40 years. According to our data the overall gastric cancer risk should be close to doubled. Thus, Helsingen found 10 gastric cancer deaths against 5.2 expected and Krause 25 against the expected number of 11. Regretably, in some series the age at surgery is either not stated or given only as a mean with or without standard deviation, without noting whether the age at surgery was normally distributed or not.

The influence of age at surgery has previously been commented on by Brollo et al (11), who reported the risk to be increased by a factor of 2.5 in patients operated on before the age of 45 while being reduced to 0.6 in patients operated above this age. Among a series of 475 cases of gastric stump cancer, collected from the literature, Peters et al (105) found the mean age at ulcer surgery to be $39,4 \pm 11.2$ years and they noted that strikingly many patients had been operated on in their thirties.

The influence of age at surgery on the risk of dying of gastric cancer also has an application in the clinical situation when a gastric resection is considered. If the patient is under 40 years of age he will run a 25 % risk of dying during a follow-up of 25 years. The probability that the cause of death will be gastric cancer is 1/11.

Furthermore, our findings suggest that gastric ulcer patients develop their cancer after a shorter time interval than duodenal ulcer patients but that over a full life span the risks are equal. This is in accordance with what has been reported by Papachristou et al (104) from a study of 1 496 gastric cancer patients, where 30 had a gastric operation for a benign condition more than five years earlier. The interval between gastric surgery and gastric cancer diagnosis was significantly longer for duodenal ulcer than for gastric ulcer patients. This could explain why clinical follow-up studies performed between 15 and 30 years postoperatively, like Helsingen & Hillestad's and our own, show a higher proportion of cancers after gastric than after duodenal ulcer operations, while in autopsy studies (60, 79, 134) and clinical follow-up studies after very long intervals, like Krause's, no differences between the two types of ulcer patients regarding the risk of dying from gastric cancer could be detected.

The reason for giving a mathematical expression for the risk of dying from gastric cancer during a five-year interval (Fig 1) is to offer the clinician a possibility of estimating the risk for a given patient. The figures should be used with caution as calculations are based on small numbers. Still, it gives an idea of how the risk changes with the length of the interval. The risk stated by the equation takes the patient's age at surgery into account fairly well since the mean observation time for patients operated on before the age of 40 was 26 years. However, it has not been possible to calculate separately the risks for duodenal and gastric ulcer patients.

In the normal population gastric cancer is an age specific disease, where the risk of dying of gastric cancer is clearly dependent upon the age of the patient. In the present series of operated patients no such age specific relative mortality could be found. This might indicate that cancer in the operated stomach is a specific disease where the operation is one important causative factor. However,

there are no data available on the risk of developing gastric cancer in peptic ulcer patients who have not been subjected to surgical treatment.

III. CANCER IN THE OPERATED STOMACH. A CLINICAL STUDY OF 61 PATIENTS.

SUMMARY

From 1970 to 1980, 39 patients with advanced gastric cancer and 22 with early gastric cancer in a previously operated stomach were diagnosed. Among patients with advanced cancer the age at primary surgery varied between 25 to 68. No early cancers were been diagnosed in patients older than 50 years of age at primary surgery. The length of the so called free interval decreased with increasing age at surgery for patients with advanced cancer. Such a relation could not be identified in early gastric cancer patients where the induction time regularly seems to be around 23 years irrespective of age at surgery.

The prognosis for patients with early gastric cancer was good. Survival for patients with advanced cancer was dependent on the stage of the disease. For 11 patients with advanced cancer restricted to the gastric wall without penetration of the serosa the estimated 5-year survival rate was 55 ± 20 %. In 28 patients with a more advanced stage of cancer a 9 ± 5 %, 5-survival rate was found. Although the number of patients in our series was small the results indicate that the poor prognosis after surgical treatment for advanced cancer in the operated stomach could be due to late diagnosis.

Five-year survival after diagnosis of advanced cancer is reported to be very low (39, 105, 107, 148). This could be due either to late diagnosis or to the fact that cancer in the operated stomach is a highly malignant tumor. If the poor prognosis is due to late diagnosis, intensified efforts for early diagnosis should be recommended but if cancer in the operated stomach is an incurable disease such efforts could be questioned. Since the introduction of fiberoptic gastroscopes it has been possible to diagnose early gastric cancer in the operated stomach (32, 33, 91, 95, 103, 114, 117, 124, 125, 126). Gastroscopy has been available at the Department of Surgery in Lund since 1968 and during the seventies we have repeatedly recommended wide indications for gastroscopy in patients with upper gastrointestinal symptoms especially in those who earlier had been submitted to gastric surgery. The aim of this study was to ascertain if our policy has influenced long-term survival.

MATERIAL AND DEFINITIONS

1. The series

All patients treated at the Department of Surgery in Lund, Sweden, from 1970 to 1980 for gastric cancer and who, at least five years before the diagnosis of gastric cancer, had been operated on for a benign gastroduodenal disease with a gastric resection or a gastroenterostomy alone were included in this study. Thirty-nine patients with advanced gastric cancer (AGC) and 22 with early gastric cancer (EGC) were treated during the period. Fifteen of the 22 EGC:s were found during the screening for cancer described in IV. All hospital records have been reviewed. All histological specimens have been reviewed by E.H.

2. Histological classification, tumor staging

Early gastric cancer (EGC) is defined according to the Japanese nomenclature as an adenocarcinoma, limited to the mucosa or submucosa with no penetration into the main muscle layer of the stomach (38). Presence of lymph node metastases does not influence the classification. All cancers penetrating into or beyond the main muscle layer are classified as advanced (AGC).

The histological type of adenocarcinoma has been classified according to Laurén (83) as being diffuse, mixed or intestinal.

After reviewing the surgical reports and the histological specimens the tumors were staged according to a modified TNM classification system.

Stage I is defined as EGC resected for cure.

Stage II: Tumor restricted to gastric wall but which does not penetrate through the serosa. Lymph node metastases accepted in the immediate vicinity of the tumor. No distant metastases. Tumor resected for cure with satisfactory margins.

Stage III: Tumor penetrates through the serosa with or without invasion of contiguous structures. Tumor resected for cure with satisfactory margins. Metastases to lymph nodes around the coeliac axis and its branches accepted if removed and further involvement could be judged as unlikely. No distant metastases.

Stage IV: Any tumor stage not resected for cure. Distant lymph node or organ metastases.

3. Surgical principles

Surgical treatment was planned after thorough, if necessary repeated, endoscopic examinations of the gastric remnant. Special care was taken to determine the extent and the superficial spread of the disease by inspection and multiple biopsies for histological examination. If the patient was believed to have an EGC a re-resection with Roux-en-Y reconstruction was planned. This was possible in 21 out of 22 cases where the cancer was located close to the anastomosis. The aim was a free margin of at least 3-4 cm and a lymph node dissection along the lesser curvature. Patients with advanced cancers were routinely scheduled for curative total gastrectomy, including lymph node dissection along the coeliac axis and its branches.

4. Statistical methods

The χ^2 method with Yates correction, or the rank sum test (Mann-Whitney) were used to test differences between groups. Survival was computed according to the life table method of Kaplan-Mayer (69). Postoperative deaths are always included. The standard error of the cumulative survival rate was estimated by Greenwood's approximation. When comparing survival curves the log rank test has been used (24, 25).

RESULTS

Indications for primary surgery, type of operations performed, length of free interval and age at diagnosis for this series are given in Tables I and II. The findings are similar to those in the patient series described in I. No significant differences could be found between patients with AGC and EGC. The age at primary gastric surgery is shown in Fig 1. Some 30 % of the patients were 40 years of age when operated on for their benign gastroduodenal disease. All patients with EGC had their primary gastric operation performed before the age of 51.

TABLE I

TYPE OF PRIMARY OPERATION AND ULCER DISEASE

		BI	BII	GE	DU	PU	GU	Misc.
Early cancer	n = 22	-	21	1	14	1	6	1
Advanced cancer	n = 39	4	32	1	22	1	14	2

No significant differences between groups (χ^2).

DU = duodenal ulcer, PU = pyloric ulcer, GU = gastric ulcer, Misc. = miscellaneous diagnoses.

TABLE II

MEDIAN AGE AT DIAGNOSIS AND LENGTH OF FREE INTERVAL

		Median age	Range	Median interval	Range
Early cancer	n = 22	63	(45-78)	23.5	(14-45)
Advanced cancer	n = 39	66	(46-87)	22	(6-45)

No significant differences between groups (Mann-Whitney U-test).

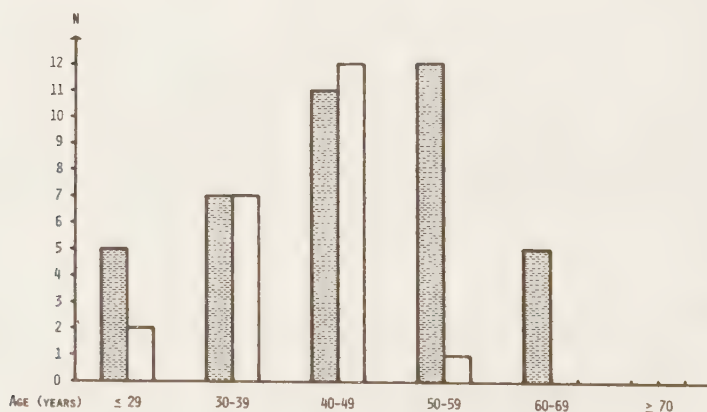


Fig 1. Number of patients in relation to age at primary operation. Shaded columns represent patients with advanced cancer and unshaded columns early gastric cancer.

The relation between age at primary surgery and time interval to cancer diagnosis for all patients with AGC is shown in Fig 2. A reverse relationship is found. The equation for the regression line could be expressed as $y = 45.9 - 0.52 \cdot X$. The correlation coefficient is -0.67 and the SD of the regression coefficient 0.096 , the regression coefficient being significantly different from zero. For EGC patients, no significant correlation between the two variables could be found. The relation between age at surgery and age at diagnosis for EGC patients is shown in Fig 3. A direct relationship was found. The equation for the regression line of the observations could be expressed as $y = 30.2 + 0.82 \cdot x$, the correlation coefficient is $+0.81$. In the subgroup of patients who were younger than 45 at primary operation and who later developed an intestinal type of cancer significantly more patients with AGC had a free interval more than 25 years (8/10) than patients with EGC (2/13, $p < 0.05$).

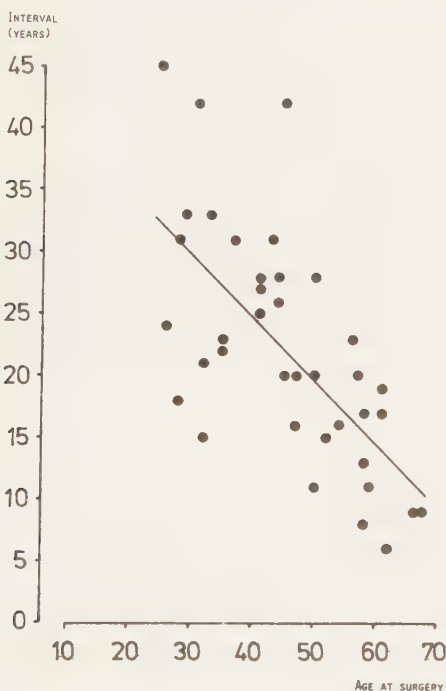


Fig 2. Age at primary surgical procedure plotted against length of interval between primary surgery and diagnosis of advanced gastric cancer. Straight line = the regression line for the observations.

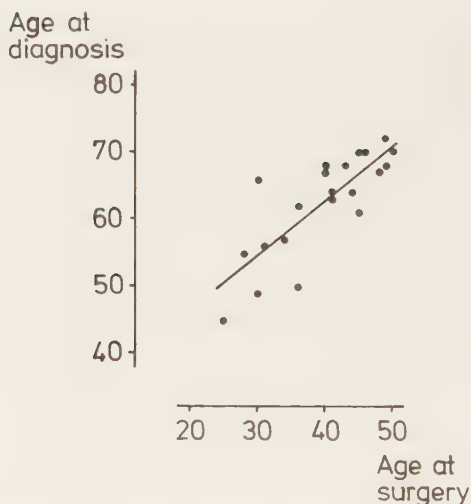


Fig 3. Age at primary surgery plotted against age at diagnosis for early gastric cancer patients. Straight line represents the regression line for the observations.

In Table III the maximum depth of penetration irrespective of distant metastases is shown. All EGC:s were localized to the mucosa, and all patients were free from lymph node metastases. We have not found any EGC:s penetrating both the mucosal and submucosal layers. Among the advanced cancers one could not be classified according to histological type. Among the classified, significantly ($p < 0.05$) more diffuse cancers invaded contiguous structures. This is also apparent when the stage of extension of the disease is determined (Table IV).

Table III. Maximum cancer depth of penetration and histological type (Laurén).

	Diffuse	Mixed	Intes- tinal	Unclassi- fied	Total
Mucosa	3	-	19	-	22
Submucosa	-	-	-	-	-
M. propria	-	-	6	-	6
Subserosa	1	-	3	1	5
Through serosa	1	5	5	-	11
Invasion of contiguous structures	7	3	7	-	17
	12	8	40	1	61

Table IV. Cancer stage and histological type.

	Diffuse	Mixed	Intes- tinal	Unclassi- fied	Total
Stage I	3	-	19	-	22
Stage II	2	-	8	1	11
Stage III	-	3	6	-	9
Stage IV	7	5	7	-	19
	12	8	40	1	61

Out of 22 patients with EGC 21 had a re-resection and one a total gastrectomy. One patient died three years postoperatively of a pulmonary embolus. Autopsy showed no recurrence. All other 21 patients were alive June 1, 1982. During follow-up two patients had local recurrences within two years and gastrectomies were then performed. In both cases the recurrent tumor was restricted to the mucosa.

Among patients with AGC 15 curative total gastrectomies, six curative re-resections, six palliative total gastrectomies and one palliative re-resection were performed. Eleven patients were either not operated on or had only an exploratory laparotomy. There were three postoperative deaths during the hospital stay, two after curative total gastrectomy (on the second and the third postoperative day, both of acute myocardial infarction) and one after exploratory laparotomy. The curative resectability was consequently 54 %, the palliative resectability 18 % and the postoperative mortality 8.5 %.

Only patients with AGC have been included when calculating survival. Survival curves were calculated from all patients with AGC and for resected patients, and patients in stages II and III+IV, respectively. The overall five-year survival rate was 22 ± 7 % (SD), and for the resected patients 30 ± 9 %. For patients in stage II of the disease 55 ± 20 % and for patients in stage III+IV 8.6 ± 5 % were estimated to survive five years. The survival curves for stage II and III+IV differ significantly ($p < 0.01$). It was not possible to differentiate survival in stages III and IV by adding other data such as histological type, depth of growth, and age at surgery.

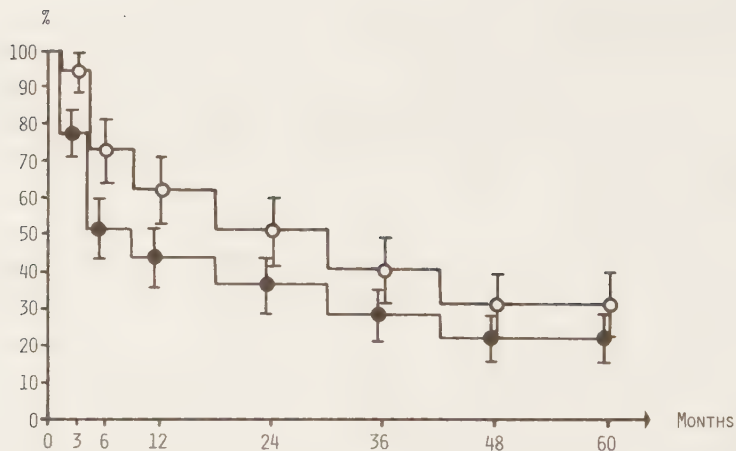


Fig 4. Estimated survival for patients with advanced gastric cancer in relation to length of follow-up, where ●—● represents the total series and ○—○ represents resected patients. Bars = SD.

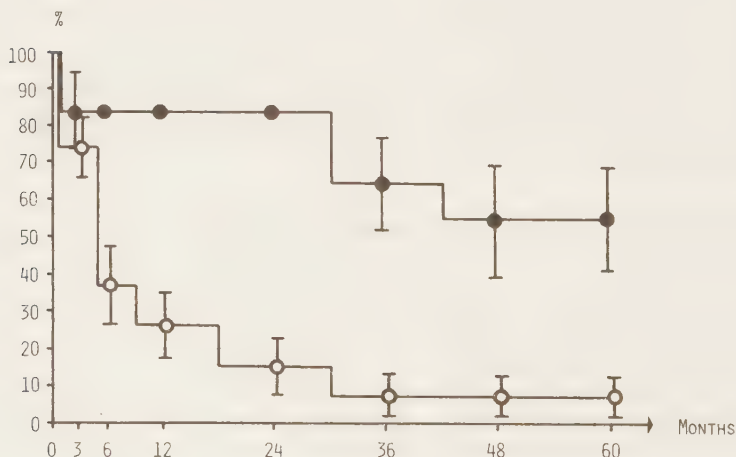


Fig 5. Estimated survival for patients with advanced gastric cancer in relation to length of follow-up. ●—● represents patients in stage II and ○—○ patients in stages III or IV of the disease. Bars = SD.

DISCUSSION

Some authors have claimed that the risk of developing gastric stump cancer is increased only after B II-resection (28, 95, 122). On the other hand, Domellöf (32, 33, 35) states that there is no difference. In the series described in II three out of 24 patients had cancer after a B I-reconstruction. The risk was found to be of the same magnitude after a gastroduodenostomy as after gastrojejunostomy. In this series another four patients were diagnosed with AGC in the gastric remnant after B I-resection. Since we do not know the distribution between B I- and B II-operations in the original patient series of patients described in this report, we cannot answer the question of whether or not stump cancer is more common after B I-surgery. It can not be discounted, however, that the risk of developing gastric cancer is also increased after gastric resection with a gastroduodenostomy.

The influence of the type of ulcer disease is open to discussion. In several other series relatively more patients have been operated on for gastric ulcer than for duodenal ulcer (48, 56, 101, 107). Deaths from gastric cancer in gastric ulcer patients occurs significantly earlier compared to duodenal ulcer patients (II). If the development of gastric cancer after duodenal ulcer surgery is delayed, as suggested in II, by 25-30 years the majority of duodenal ulcer patients may be so old at the time when cancer has developed that patients are simply not considered operable and therefore not referred for surgery. Calculations of risks of developing gastric cancers from surgical series could thus be biased.

The age at primary surgery has earlier been shown to be associated with the risk of developing cancer (II). The age at primary surgery in this clinical series did not differ from that seen in the series in I. Many patients were referred to the Department from other hospitals. We do not know from which age groups they were selected and therefore no conclusions can be drawn.

The length of the free interval in relation to age at surgery has earlier been studied by Schmidt et al (124). On the basis of 40 cases he calculated the regression coefficient and found it to be -0.525 , or the same as in our series from patients with AGC. The finding may partly be explained by the fact that duodenal ulcer patients developed cancer after a longer interval than gastric ulcer patients, and with increasing age an increasing number of gastric ulcer patients are submitted to surgery. For EGC patients such a relation is not apparent. A good correlation was found between age at surgery and age at diagnosis with a regression coefficient close to one (0.82). This suggests that the length of the free interval for the typical EGC is 20-24 years irrespective of age at surgery. This calculation is based on a relatively small number of patients and the results should be confirmed. One reason why we have not found any patients with EGC operated on after the age of 50, but 13

AGC:s, may be due to the fact that screening, where most EGC:s were found, started with a minimum interval of 12 years after surgery. However, most other reported cases (32, 33, 34, 114, 125) had their primary resection performed before the age of 55 and the EGC diagnosed 18-33 years later. One conceivable explanation is that the EGC stage, may in elderly patients is short, and therefore difficult to detect.

In this series no differences were found in the localization of AGC of diffuse/mixed type compared to the intestinal type but AGC:s of the former type were in a more advanced stage when diagnosed, suggesting that diffuse and mixed carcinomas have a more rapid growth pattern or causes less symptoms.

We found no early cancers penetrating the submucosal layer. A few cases have been described (32, 103, 126) and we have seen two in combination with advanced cancer but separately localized. When EGC is diagnosed in the non-operated stomach considerably more penetrate into the submucosa (66, 150). Multiple routine biopsies in a restrictive predelicting area around the anastomosis (53) may explain why all EGC:s were found to be limited to the mucosa.

For treatment of EGC total gastrectomy has been recommended (125). On the basis of our experience with follow-up of, at most nine years, results after simple re-resection have so far been gratifying. It may therefore be sufficient to perform a less mutilating procedure associated with lower postoperative mortality. With careful preoperative gastroscopic and histological examinations it has been possible to establish the oral borderline of EGC in most cases. A 10 % local recurrence rate indicates, however, that we were not successful in all patients. With the aid of film, photos and biopsies taken during gastroscopy we are convinced that the identification of the borderlines of EGC can be established more exactly. However, as long as part of the gastric remnant is left in situ recurrence is a reality but may be found at a curable stage if patients are scheduled for regular yearly follow-ups.

The chance of surviving a cancer operation is dependent upon the extension or the stage of the disease. In many surgical reports on survival after gastric cancer surgery the only description of stage given is whether or not the tumor was resectable. Better classification procedures have often been recommended but seldom used (120). Our estimated five-year survival rate differs from that reported by Peitsch & Burkhardt (108). After reviewing the literature they found a collective five-year survival rate of 1.38 % among 2 390 patients. Those results are similar to what we found in patients with stage III and IV disease. It is difficult to analyse why our patients had a better prognosis. Cancer of the intestinal type is associated with a better five-year survival (83). In two reports 40-52 % of patients had an advanced cancer of the intestinal type which is similar to our findings (57, 137). Thus difference in

cancer type does not explain differences in long-term survival. In the above mentioned series the resectability was 46 % compared to 73 % in our series. This may indicate that more patients in our series were diagnosed at an earlier stage of the advanced disease.

In conclusion an increased awareness of the problem with cancer in the operated stomach and wide indications for gastroscopy and biopsy may have contributed to improving five-year survival rates. We found no indications that advanced cancer in the operated stomach is an incurable disease.

IV. SCREENING FOR CANCER IN THE OPERATED STOMACH

SUMMARY

From 1930 to 1960 1 575 patients were operated on for benign gastroduodenal disease at the Department of Surgery in Lund, Sweden. At the end of 1973, 796 were still alive. During the last half of 1972 and the first of 1973 these patients were offered screening for gastric cancer with gastroscopy and biopsy. Among those 357 who came for the examination four advanced and seven early gastric cancers were diagnosed. A second screening was performed 1978/1979. During the interval between the two screening examinations further one advanced and seven early cancers had been detected. Out of the 297 possible participants 176 came for the second screening which revealed two advanced and one early gastric cancers. Thus, during seven years follow-up at a mean of 19-26 years after surgery for benign gastroduodenal disease seven advanced and 15 early cancers were detected among 357 patients. The annual incidence of advanced gastric cancer during the period was 0.28 % against the expected 0.14 %. Gastric cancer mortality rate was found to be the same among the 357 screened patients as among the 439 patients who did not attend the screening examinations. In spite of the fact that 15 early cancers have been resected among the screened patients and only two among the not screened, an effect on cancer mortality of detecting early gastric cancer is not yet apparent after six to seven years' observation.

The incidence of gastric cancer among symptomatic patients earlier operated on for benign gastroduodenal disease is reported to be so high that gastroscopy and biopsy should always be recommended (20, 23). The role of upper gastrointestinal symptoms as a selector for participation in screening examinations has not been investigated. The results in different series where patients have been offered screening varies. Domellöf et al (32, 33) found six advanced and four early cancers among 288, Schrumpf et al (125) one advanced and three early cancers among 108, Rösch (116) one early cancer among 117 and Savage et al (123) no cancers among 65 screened patients. Selection may play a role in explaining some of these differences since patients with symptoms may take the opportunity to participate in screening more often than patients free from symptoms, especially if the invitation clearly states that the purpose of the investigation is to detect cancer. The accumulated experience from screening examinations is that cancer is detected more frequently than could be expected among non-operated patients of the same age. However, it has not yet been shown whether or not screening contributes to a decrease in cancer mortality.

MATERIAL AND METHODS

1. The series

At the Department of Surgery in Lund, Sweden, 1 575 patients were operated on for benign gastroduodenal disease from 1930 to 1960 and 1 403 could be traced after leaving the hospital. At the end of 1973, 796 were still alive. During the last part of 1972 and first half of 1973 682 patients living within an area of 300 km from the hospital were offered screening for gastric cancer with gastroscopy and biopsy. Three hundred and sixty-three came to the examination. In six the gastroscopy failed. Thus 357 (45 %) have been screened and 439 (55 %) were not screened and can be regarded as controls.

Table I. Screening for gastric cancer with gastroscopy and biopsy 1978/1979.

	Sex			Indications for surgery			
	Male	Female		DU	PU	GU	Misc
Alive 31/12-73	796						
Examined 72/73	357	37		236	16	98	7
Not examined							
72/73	439	349	90**	299	10	117	13

** = $p < 0.01$. DU = duodenal ulcer, PU = pyloric ulcer, GU = gastric ulcer, Misc = miscellaneous diagnoses.

As shown in Table I significantly less women ($p < 0.01$) came for screening. The distribution of different ulcer diseases among

screened and not screened patients was the same. The latter group of patients was significantly older ($63.3 \pm 9.8/66.1 \pm 11.5$ years, $p < 0.05$, tested with χ^2 for age groups) and had a longer interval since the operation ($19.4 \pm 4.7/21.7 \pm 6.7$ years, $p < 0.01$, tested with χ^2 for interval groups). No differences between the two groups could be detected when age at primary surgery was tested (Fig 1). The most important factor increasing the risk of dying of gastric cancer in an interval around 20 years after gastric surgery is the primary ulcer disease and age at operation (II). No significant differences were found between the screened and not screened patients in these aspects.



Fig 1. Age at primary surgery for patients screened for gastric cancer with gastroscopy and biopsy in 1972/1973. Open columns represent screened and shadowed not screened patients. Upper parts of columns represent women.

Between 1972/1973 and 1978/1979 the indications for repeated endoscopic examinations were based on clinical praxis, i.e. patients complaining of symptoms have been examined and patients with severe atypia in routine biopsies were, after an initial re-examination, followed yearly.

During the last half of 1978 and the first of 1979 patients participating in the first screening were offered a second examination. Out of the 296 who were still alive 176 (59 %)

participated in the second screening (Table II). Follow-up terminated October 1, 1979.

Table II. Screening for gastric cancer in 1978/1979

Initially screened 1972/1973	357	
Dead at follow-up	60	
Withdrawn alive	1	
Alive 1979	296	
Examined 1978/1979	175	
- Reoperated for advanced cancer		1
- Reoperated for early cancer		13
- Reoperated for benign conditions		7
- Not reoperated		155
Not examined	121	

2. Definitions

Early gastric cancer (EGC) is defined as an adenocarcinoma limited to the mucosal and submucosal layer of the gastric wall.

Advanced gastric cancer (AGC) is defined as an adenocarcinoma that penetrates the submucosal layer and grows into the main muscle layer (muscularis propria).

After examination the surgical report and histological specimens tumor was staged according to a modified TNM system (III).

3. Statistical methods

Chi² analyses were used to test differences in distributions between groups.

RESULTS

Clinical data for patients where gastric cancer was diagnosed in the 1972/1973 examination is given in Table III.

TABLE III
GASTRIC CANCERS DETECTED AT FIRST SCREENING 1972/1973

SEX	ULCER DISEASE	AGE AT SURGERY	INT. TO DIAGNOSIS	SYMPTOMS	GASTRO-SCOPY	SURGERY	CANCER TYPE	STAGE	SURVIVAL
K.E.	male	d.u.	50	11	alteration of earlier pg. spt.	cancer	expl. lap. mixed	IV	3 months
G.N.	male	g.u.	32	21	free of spt.	cancer	total gastrect.	III	11 months
T.O.	male	g.u.	26	24	pg. spt.	cancer	subtotal gastrect.	II	alive 1/6 1982
A.A.	male	g.u.	44	28	alteration of earlier pg. spt.	cancer	not op., distant metast.	IV	1 month
R.O.	female	d.u.	30	36	pg. spt.	severe ERG	re-resection	I	alive 1/6 1982
E.N.	male	d.u.	45	16	pg. spt.	severe ERG	re-resection	I	alive 1/6 1982
T.W.	male	d.u.	36	14	pg. spt.	severe ERG	re-resection	I	alive 1/6 1982
E.L.	male	g.u.	50	20	free of spt.	severe ERG	re-resection	I	alive 1/6 1982
G.N.	male	d.u.	44	20	free of spt.	severe ERG	re-resection	I	alive 1/6 1982
F.L.	male	p.u.	49	23	pg. spt.	severe ERG	re-resection	I	alive 1/6 1982
E.N.	male	g.u.	40	27	free of spt.	mod. ERG + polyp	re-resection	I	alive 1/6 1982

D.u. = duodenal ulcer, p.u. = pyloric ulcer, g.u. = gastric ulcer, pg. spt. = postgastrectomy symptoms, ERG = endoscopic reflux gastritis, AGC = advanced gastric cancer, EGC = early gastric cancer, intest. = intestinal. Definitions of Stage I-IV see text.

Four patients with AGC and seven with EGC were found at the first screening. The distribution of ulcer disease, type of operation, age at primary surgery and length of time interval between operation and diagnosis and the number of patients free of symptoms did not differ significantly from screened patients without detected cancer. Two out of four patients with AGC had experienced an alteration in their postgastrectomy symptoms between one and six months prior to the examination. Both these cancers were inextirpable. One patient free of symptoms survived 11 months after total gastrectomy. One patient with postgastrectomy symptoms had a small but typically advanced cancer near the anastomosis. He is still alive, without evidence of recurrence in the middle of 1982, after a curative subtotal gastrectomy.

Seven patients with EGC were diagnosed. Four had had mild postgastrectomy symptoms since the primary operation. Three had postprandial nausea and bile-stained vomitings and one postprandial pains and early dumping. Three were free from symptoms. Gastroscoically, six out of seven EGC patients showed severe endoscopic reflux gastritis and one had moderate endoscopic reflux gastritis and a polyp close to the anastomosis (for definitions see V).

During the follow-up period until the second screening in 1978/1979 one further patient with AGC and seven with EGC were found. At the second screening two AGC and one EGC were diagnosed. Clinical data are given in Table IV.

One patient had died of acute myocardial infarction in 1975 and autopsy showed a 2 x 3 cm advanced cancer near the anastomosis. Two patients with AGC were detected at the second screening. One had experienced an alteration in quality of earlier postgastrectomy symptoms three months earlier and the other claimed to be free from symptoms. After curative subtotal gastrectomy they are both still alive in the middle of 1982.

Five out of the eight EGC diagnosed had severe atypia at the initial screening and had, from the beginning, been scheduled for regular follow-ups. These five cancers were diagnosed one to three years later. Two further EGC were diagnosed at gastroscopy and biopsy because of symptoms. One of these complained of postgastrectomy symptoms and was operated on because of severe bleeding after biopsy. The other patient was operated on because of "uncharacteristic upper abdominal pain", gallbladder disease and severe atypia in the anastomosis. It was impossible to differentiate the symptoms as being due to chronic cholecystitis or severe postoperative reflux gastritis. Finally one EGC was diagnosed at the second screening, this patient was free from symptoms.

TABLE IV
CANCERS DETECTED DURING FOLLOW-UP AFTER FIRST SCREENING

SEX	ULCER DISEASE	AGE AT SURGERY	INT. TO SYMPTOMS DIAGNOSIS	IND. FOR GASTRO-SCOPY	GASTRO-SCOPY FINDINGS	SURGERY	CANCER TYPE	STAGE	SURVIVAL
S.A.	male	52	22	-	-	autopsy	AGC intest.	II	-
O.O.	male	56	23	alteration of earlier pg. spt	screening cancer 78/79	subtot. gastrect.	ACC intest.	III	alive 1/6 1982
S.A.	male	29	33	free of spt.	screening cancer 78/79	subtot. gastrect.	AGC intest.	II	alive 1/6 1982
H.S.	male	41	23	free of spt.	follow-up 1976 ERG	subtot. gastrect., recurr. 1978, tot. gastrect.	EGC intest.	I	alive 1/6 1982
E.A.	male	41	22	free of spt.	screening "normal" 78/79	subtot. gastrect.	ECC diffuse	I	alive 1/6 1982
S.W.	male	46	22	free of spt., occult g.i. bleed.	follow-up 1974 ERG	subtot. gastrect.	EGC diffuse	I	alive 1/6 1982
K.K.	male	43	26	pg. spt.	follow-up 1975 ERG	subtot. gastrect.	EGC intest.	I	alive 1/6 1982
S.N.	male	31	25	alteration of earlier pg. spt.	symptoms 1975 ERG	emerg. op., bleed, aft. biopsy	EGC intest.	I	died 1978 pulm. embolism
H.N.	male	45	25	pg. spt.	follow-up 1976 ERG	subtot. gastrect.	EGC intest.	I	alive 1/6 1982
A.A.	male	30	19	pg. spt. and/or chron. cholecyst.	symptoms 1975 ERG	subtot. gastrect. + cholecyst.	EGC intest.	I	alive 1/6 1982
R.J.	male	34	23	free of spt.	follow-up 1973 ERG	subtot. gastrect.	EGC intest.	I	alive 1/6 1982

During seven years of follow-up, four out of seven diagnosed AGC patients have died. The corresponding numbers among not screened patients is six out of six. The annual incidence of AGC among screened patients can thus be calculated to 0.28 % against the expected 0.14 % (age and sex corrected according to Cancer Incidence in Sweden 1975 (17)). The annual incidence of early gastric cancer was 0.6 %.

In II we calculated the risk (Q) of dying of gastric cancer during a specific five-year interval. Actuarial data could be fitted to the exponential equation $\ln Q = -6.49 + 0.0678 \cdot T$ (T = years after gastric surgery). We transformed our seven year follow-up data for screened and not screened patients to the risk of dying during a five-year interval. For screened patients the observed risk was 0.0080 and for not screened patients 0.0098. The mean interval 1972/1973 was 19.4 and 21.7, respectively. As seen in Figure 2 the observed risks both among screened and not screened patients fit well with that given by the equation.

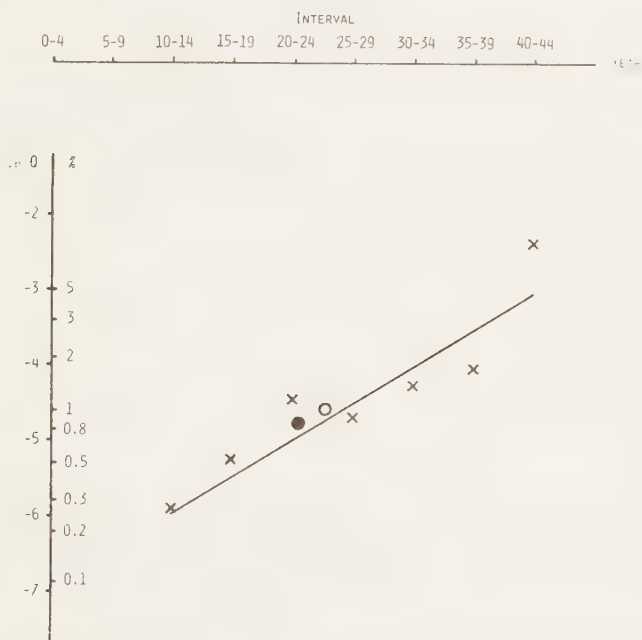


Fig 2. Observed risks (Q) of dying during a 5-year interval for screened ● and not screened ○ patients in relation to mean length of the interval for the two groups during follow-up. X indicates observations from the entire series of 1403 patients described in II and the straight line the regression line for these observations.

In the corresponding manner the incidence of EGC during a five-year interval was calculated. All EGC diagnosed within five years after the first examination in 1972/1973 were included, and the incidence calculated on the basis of 353 examined patients (e.g. four patients with AGC were excluded). Data could be fitted to the exponential equation $\ln q = -5.92 + 0.135 \cdot x$ ($r = 0.980$, $SD_b = 0.020$).

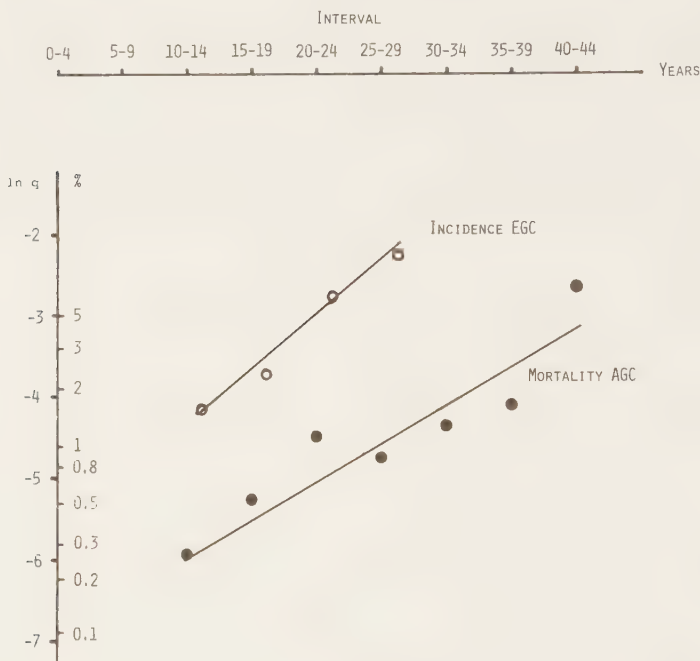


Fig 3. The risk (q) of dying in gastric cancer during specific five-year survivals is indicated by filled dots (●) (II). The incidence of early gastric cancer diagnosed in 353 screened patients during specific five-year intervals is indicated by open dots (○). The straight lines represent the regression lines for the observations.

The annual mortality rate in gastric cancer for screened patients was 0.16 % against expected 0.08 and for not screened patients 0.20 % against an expected rate of 0.09 % (age and sex corrected according to causes of death in Sweden 1977 (20)). Thus, both annual incidences and mortality rates among the studied groups of patients were double the expected.

DISCUSSION

As other authors have stated earlier we want to stress the importance of an alteration in quality and quantity of the postgastrectomy symptoms as an important indication of a possible malignant degeneration in the operated stomach (19, 23, 124). The incidence of AGC and EGC among screened patients in this series does not differ substantially from that found by other Scandinavians (32, 33, 125, 136). When calculating the annual incidence of gastric cancer among patients during follow-up we consider it necessary to separate advanced cancer from early cancer, if figures are to be compared with that of the general population. We do not know if all EGC proceed to an advanced stage, and proportionally more EGC:s are found among screened patients operated on for benign gastroduodenal disease than in the general population. The annual mortality from among screened and not screened patients was twice that expected during a six to seven year follow-up, and thus we cannot support those who claim that the risk is equal to that of the general population (14, 36, 57). Nineteen to 29 years postoperatively the operated stomach seems to be a precancerous condition.

The annual incidence of early gastric cancer was found to be 0.6 % and this can only be compared to other screening series. Schrumpf et al (125) series has been followed up after three years (136). Initially they found three EGC out of 108 patients. No new EGC:s were found during follow-up which indicates an annual incidence of around 1 % which is similar to our findings.

The mortality rate in AGC among screened and not screened patients in our series was practically the same despite the fact that 15 EGC had been operated among screened patients and only two among not screened. Seven years of follow-up may be too short a period to detect any effect on mortality. The mean age for all patients living at the end of 1979 was 69 years and the life expectancy thus limited. It may therefore be difficult to establish an effect of screening on cancer mortality.

Among screened patients we have observed an EGC incidence rate five to ten times higher than the mortality rate from gastric cancer in corresponding intervals after surgery. The difference may to some extent depend on selection of EGC patients with symptoms for screening as only six of 14 reported themselves to be free from upper gastrointestinal symptoms. Even if the true incidence of EGC should be calculated on the basis of both screened and not screened patients (which is unlikely since we actually have diagnosed two EGC:s among not screened patients) difference between EGC incidence and gastric cancer mortality is great. This strongly suggests that not all patients with EGC will die of gastric cancer. If all EGC:s rapidly proceed into advanced cancers differences in incidence and mortality rates ought to be small as patients with advanced cancer have a poor prognosis (107). The probability of an EGC in the operated stomach

remaining as an early cancer for some years seems to have been underestimated. In old patients with a limited life expectancy other therapies could perhaps be considered such as Argon lazer coagulation, as an alternative to surgical intervention (117).

Rather than finding a number of possibly innocuous EGC:s it may perhaps be more important to diagnose AGC at a curable stage. This effect of the screening procedure can be registered today. Among screened patients with AGC, three are still alive 3.5, 3.5 and 8 years postoperatively as opposed to none of the patients who were not screened for cancer.

By considering the factors shown to increase the risk of dying of gastric cancer (II) e.g. surgery at early age, operation for gastric ulcer, and an interval exceeding 15 years it might be possible to select patients for screening who run a markedly increased risk. Thus, the goal of reducing mortality from gastric cancer could possibly be reached with comparatively modest costs and efforts. However, risk factors could only be used when planning a screening examination. Patients who develop symptoms, or experience a change in their symptomatology should be subjected to gastroscopy without delay.

V. CORRELATION BETWEEN CLINICAL SYMPTOMS AND GASTROSCOPIC AND HISTOLOGICAL FINDINGS IN PATIENTS OPERATED ON FOR BENIGN GASTRODUODENAL DISEASE

SUMMARY

A series of 357 patients operated on for benign gastroduodenal disease 12 to 42 years previously was screened for gastric cancer with gastroscopy and biopsies in 1972/1973. When questioned, 31 % of the patients reported one or several symptoms referable to the upper gastrointestinal tract. The most frequent symptom was postprandial fullness, which occurred in 12 %. Bile-stained vomits were reported in 6 % of the patients. A positive correlation was found between the presence of symptoms such as postprandial epigastric fullness, nausea and pain and bile vomitings and the severity of gastroscopic findings e.g. bile reflux, redening of the mucosa and yellowish zones in close relation to the anastomosis. When the degree of different histological changes was analysed in relation to individual symptoms, significantly more severe intestinal metaplasia and atypia were found in patients who reported postprandial fullness and bile-stained vomits. These findings support the concept of the syndrome of reflux gastritis as a clinical entity with a good correlation between the clinical symptoms and gastroscopical picture.

In the clinical follow-up after gastric surgery, patients' symptoms may be classified as belonging to one or more of different syndromes: e.g. recurrence of ulcer disease, dumping, chronic afferent loop syndrome or the syndrome of postoperative reflux gastritis. Ulcer recurrence is a minor clinical problem as it is easy to diagnose and treat (23, 77). Dumping is described as a sequency of postprandial epigastric fullness, vasomotor symptoms, general muscular weakness, nausea, and diarrhoea (89). Chronic afferent loop syndrome is suspected when postprandial epigastric fullness and pain is relieved by bile vomits (26), and the syndrome of reflux gastritis when the patient experiences postprandial pain, nausea and bile vomits (145). Some of the symptoms are included in all syndromes. The main etiology of the syndromes is thought to be a postprandial reduction in plasma volume, anatomical obstruction and gastritis. After gastric surgery all these etiological factors could be operating and the patients' symptoms be due to a combination (109). To evaluate an individual symptom it is important to know its correlation to routinely used examinations such as gastroscopy and histology. Screening patients for gastric cancer in the operated stomach gave a good opportunity for such a study.

MATERIAL AND METHODS

1. The series

Three hundred and fifty-seven patients operated on for benign gastroduodenal disease 12 to 42 years previously were screened for cancer in 1972/1973. The screening programme consisted of an analysis of symptoms, physical examination, and gastroscopy with standardized biopsies. In this study four patients who were found to have an advanced gastric cancer have been excluded leaving 353 patients to be analysed.

2. Symptoms

The patients were asked if they had one or several of the following symptoms: 1) Remaining ulcer-like symptoms relieved by food or antacids. 2) Epigastric fullness in relation to meals. 3) Nausea in relation to meals. 4) Bile-stained vomits. 5) Epigastric pain in relation to meals. 6) Desire to lie down or tendency to faint after meals. If patients had other symptoms referable to the upper gastrointestinal tract these were also noted. The degree of each symptom was not noted, but the duration of the symptom was.

3. Gastroscopy

All examinations were performed by B.H. with an Olympus gastroscope type EF. Patients were premedicated with 0.5 mg Atropin i.m. and topical anaesthesia (Xylocain[®]) of the pharynx 10 min and immediately prior to the investigation, respectively.

During gastroscopy the severity of endoscopic reflux gastritis (ERG) was prospectively registered. The definitions used were as follows: ERG 0 = a normal gastric mucosa without reddening or admixture of bile to the gastric secretion. ERG 1 = mild diffuse reddening of the mucosa. ERG 2 = moderate reddening of the mucosa most pronounced on the major curve adjacent to the anastomosis, gastric secretion slightly bile-stained, gastric remnant limp and variable. ERG 3 = clear reflux of bile into the gastric remnant during the examination, reddening of the gastric mucosa around the anastomosis, a number of spots or small continuous zones of grey-yellowish mucosa in close relation to the anastomosis, somewhat rigid and fragile mucosa. ERG 4 = rigid, thin, fragile and easily bleeding mucosa covered with smeary bile-stained mucous. Reddening of the mucosa around the anastomosis. Long continuous zones or areas of grey-yellowish mucosa in close relation to the anastomosis. The appearance of superficial erosions.

Other findings registered were cancer, polyps, and ulcerations. Examples of different endoscopic findings see VI, Figures 1-8. At least four biopsies were taken from the gastric mucosa of the anastomotic region irrespective of the gastroscopic findings.

4. Histology

All biopsies have been examined by EH. For further detailed information see reference number 57.

Biopsies were routinely stained according to hematoxylin-erythrosine, van Gieson and PAS (MacManus). Six types of histological changes were registered, each in four grades (0-3). If individual biopsies taken at the same occasions varied in degree, the most severe degree was registered.

Abberations and definitions of studied histological parameters

Acute gastritis (AG). Interstitial infiltration of polymorphonuclear leucocytes within the mucosa. In grade 1 infiltration is limited to the upper third and grade 3 includes erosions and ulcerations.

Chronic gastritis without atrophy (CG). Interstitial infiltration of lymphocytes and plasma cells without signs of atrophy. In grade 1 the upper third of the mucosa is involved (superficial gastritis) and in grade 3 the mucosa is diffusly infiltrated by mononuclear cells and the mucosa appears thicker than normal.

Chronic gastritis with atrophy (CAG). Diffuse interstitial infiltration of lymphocytes and plasma cells accompanied by a reduction in number and length of glands. In grade 1 the thickness of the mucosa is reduced to approximately 2/3 of the normal. The typical example of grade 3 is gastric atrophy.

Chronic hyperplastic gastritis (CHG). A miscellaneous group with foveolar hyperplasia, intramucosal cysts, fibrosis, infiltrates of histiocytes or xanthoma cells and Russell's bodies. When several signs are present, attention is paid to the change showing the most severe alteration.

Intestinal metaplasia (IM). The occurrence of small intestinal-like mucosa with brush border, Paneth's cells and goblet cells. A quantitative estimation of mild, moderate and severe degrees.

Atypia (API). Grade 1 = localized cellular changes in surface epithelium or in one or several glands, nuclear hyperchromasia and increased cytoplasmic basophilia. Grade 2 = wide-spread cellular and glandular changes with disturbed polarity, nuclear pleomorphism, visible nucleoles and several mitoses. Grade 3 = cellular dedifferentiation, abnormal mitoses and glandular destruction or desorganization with disappearance of secretory products. Signs of infiltration through basement membranes, synonymously with adenocarcinoma.

Comments:

In the transitional stage before a lesion with certainty could be classified as adenocarcinoma the lesion only presents some of the criteria of cancer (50, 66, 70, 92, 98, 99, 102). The assessment of such a lesion varies. Despite having the entire resected specimens to investigate difficulties sometimes occur in establishing the true nature of a lesion. The problem is more evident in biopsies. Japanese investigators have, since 1971, classified biopsies in five groups where I is normal, II benign lesions with slight atypia, III borderline lesions, IV probably carcinoma, and V definite carcinoma (65). A WHO committee in 1979 agreed to use the conception of dysplasia in gastric histopathology (95). The boundaries for three grades, mild, moderate and severe, were stated and recommended for use in both biopsies and resected specimens. Nagayo (100) states that mild, moderate and severe dysplasia corresponds to the Japanese group classification II, III and IV. Our interpretation of the relations between the two classification systems and the degree of atypia used in this report is illustrated in Table I.

To be included in atypia grade 3 the findings in biopsies should at least, be interpreted as being highly probable that they were taken from an adenocarcinoma. If the certainty was judged to be less, the lesion was classified as grade 2. If the overall microscopical picture gave any suspicion of, cellular and glandular changes being reactive the degree of atypia was graded 1.

Table I

Japanese group classification 1971	I	II	III	IV	V
Atypia Hammar 1977	0	1	2	3	
Dysplasia WHO-committee 1979	0	Mild	Moderate	Severe	Cancer

Biopsies were interpreted and graded twice without knowledge of clinical data or the result of preceding investigations. We have in this report for each of the six different histological changes summed up the result from the two examinations. Each histological parameter thus get a score varying from 0 to 6. The results are given in Table II for general information. In biopsies it is difficult to judge whether or not a chronic gastritis is combined with atrophy. If a chronic gastritis was found, the pathologist had to decide. The most difficult cases could in one investigation be judged to be accompanied by atrophy and in the other not.

Table II. Histological findings in biopsies among 353 screened patients 1972/1973.

		AG	CG	CAG	CHG	IM	API
Normal	Score 0	31	76	166	1	207	86
Mild	Scores 1-2	96	120	114	41	66	229
Moderate	Scores 3-4	198	141	58	253	59	31
Severe	Scores 5-6	28	16	15	58	21	7
Total		353	353	353	353	353	353

5. Statistical methods

Chi² analysis and the Mann-Whitney U-test were used to test differences between groups.

RESULTS

When questioned, 110 patients out of 353 (31 %) reported one or several symptoms referable to the upper gastrointestinal tract (Table III).

TABLE III

CLINICAL DATA AND SYMPTOMS

Syptom No.	1	2	3	4	5	2-5	6	Upper g-i spt.	Free from symptoms
Male	14	37	20	15	21	52	23	91	225
Female	2	5	6	6 *	8 *	13	5	19 *	18
B I	5	2	4	4	2	6	3	15	27
B II	11	40	22	17	26	58	25	94	214
GE	-	-	-	-	1	1	-	1	2
DU	12	27	15	10	21	44	21	77	158
GU	2	11	8	9	5	16	5	25	70
Misc.	2	4	3	2	3	3	2	8	15

Symptom No 1 = ulcerlike symptom, 2 = postprandial fullness, 3 = postprandial nausea, 4 = bile stained vomits, 5 = postprandial pain, 6 = desire to lie down and rest or tendency to faint after meals. * $p < 0.05$.

B I = Billroth I, B II = Billroth II, GE = gastroenterostomy, DU = duodenal ulcer, GU = gastric ulcer, Misc. = miscellaneous diagnoses.

Eight per cent of patients had experienced the same symptoms since the operation. Only 12 had previously been free from symptoms and during the last five years prior to the examination noticed various postgastrectomy symptoms. Two out of seven patients who reported epigastric pain without relation to meals had a pancreatic cancer diagnosed within a year. The incidence of an individual symptoms varied between 4.5 to 12 %. When analysing the influence of sex, type of operation an original ulcer disease on the distribution of symptoms significantly more symptoms were found in women. The other factors were not important for the occurrence of the clinical symptoms.

The degree of ERG was correlated with all studied symptoms except for the desire to lie down and rest after meals. In Table IV the degree of ERG is given for patients with and without symptoms.

TABLE IV

CORRELATION BETWEEN REPORTED SYMPTOMS AND GRADE OF
ENDOSCOPIC REFLUX GASTRITIS (ERG) IN 353 PATIENTS

	ERG	0	1	2	3	4	
Ulcerlike symptoms	N= 16	2	10	4	-	-	
Ulcerlike symptoms lacking	N=337	26	96	127	70	18	p <0.01
	ERG	0	1	2	3	4	
Postprandial fullness	N= 42	2	6	12	15	7	
Postprandial fullness lacking	N=311	26	100	119	55	11	p <0.001
	ERG	0	1	2	3	4	
Postprandial nausea	N= 26	3	1	9	7	6	
Postprandial nausea lacking	N=327	25	105	122	63	12	p <0.01
	ERG	0	1	2	3	4	
Bile stained vomits	N= 21	1	1	9	7	3	
Bile stained vomits lacking	N=332	27	105	122	63	15	p <0.01
	ERG	0	1	2	3	4	
Postprandial pain	N= 29	2	5	9	7	6	
Postprandial pain lacking	N=324	26	101	122	63	12	p <0.05
	ERG	0	1	2	3	4	
Any of spt. 2, 3, 4, 5	N= 65	4	9	23	19	10	
None spt. 2, 3, 4, 5	N=288	24	97	108	51	8	p <0.001
	ERG	0	1	2	3	4	
Desire to rest after meals	N= 28	3	6	8	9	2	
Desire to rest after meals lacking	N=325	25	100	123	61	16	NS

(Mann-Whitney U-test)

Patients with ulcer-like symptoms were few but had less ERG than patients lacking that symptom. None had a recurrent ulcer. Postprandial fullness was the symptoms that best correlated to an increased degree of ERG ($p < 0.001$). Patients who experienced one or several of the symptoms numbers 2 to 5 also had significantly more ERG ($p < 0.001$). This can be expressed as the probability of having severe

endoscopic reflux gastritis (ERG 3-4) when the patient reported postprandial fullness, nausea or pain or bile-stained vomits was 45 % and the probability of not having severe endoscopic reflux gastritis (ERG 0-2) when these symptoms were lacking was 80 %.

Patients with postprandial nausea or pain had the same distribution of scores in the six different types of histological changes studied as patients that lacked those symptoms. Patients with postprandial fullness had significantly higher scores for CAG, CHG, IM and API ($p < 0.05/p < 0.01$) as shown in Table V.

TABLE V

CORRELATION BETWEEN REPORTED SYMPTOMS AND DEGREE OF HISTOLOGICAL FINDINGS IN BIOPSIES

Symptoms	N	AG	CG	CAG	CHG	IM	API
1. Ulcerlike	16	$p < 0.05$	NS	NS	NS	NS	NS
2. Postprandial fullness	42	NS	NS	$p < 0.01$	$p < 0.05$	$p < 0.05$	$p < 0.05$
3. Postprandial nausea	26	NS	NS	NS	NS	NS	NS
4. Bile stained vomits	21	NS	NS	NS	NS	$p < 0.05$	$p < 0.01$
5. Postprandial pain	29	NS	NS	NS	NS	NS	NS
2-5 One or more of spt. 2-5	65	NS	NS	$p < 0.01$	$p < 0.05$	$p < 0.05$	NS
6. Desire to rest after meals	28	NS	NS	NS	NS	NS	$p < 0.05$

Patients with a symptom compared with patients lacking that symptom. Mann-Whitney U-test.

All symptoms except ulcerlike correlated to higher degree of histological changes. NS = Not Significant.

Patients with one or more symptoms numbers 2-5 had higher scores for CAG ($p < 0.01$), CHG ($p < 0.05$) and IM ($p < 0.05$). Those who had a desire to lie down and rest after meals had higher scores for API ($p < 0.05$) when compared with patients that lacked the respectively symptom. Ulcer-like symptoms were associated with a lower degree of AG ($p < 0.05$). The symptoms correlating to the degree of atypia were postprandial epigastric fullness and bile-stained vomits and the desire to lie down and rest after meals. The probability of having

early gastric cancer when the patient reported bile-stained vomits was 14 % (3/21) and the probability of not having early gastric cancer when the symptom was lacking was 98.8 % (328/332) (Table VI).

TABLE VI

SCORES IN ATYPIA IN BIOPSIES FROM PATIENTS
WITH AND WITHOUT BILE STAINED VOMITS

	No. of patients	Atypia						
		0	1	2	3	4	5	6
Bile stained vomits	21	1	7	7	2	1	2	1
No bile stained vomits	332	85	105	110	18	10	1	3

Mann-Whitney $p = 0.007$

DISCUSSION

By analysing this series it is not possible to calculate the true incidence of different symptoms among patients operated on for benign gastroduodenal disease since we lack information from those patients (55 %) who did not attend the screening. Five to eight years after surgery Goligher et al (47) assessed the results after partial gastrectomy. They found an incidence of individual upper gastrointestinal symptoms such as epigastric fullness, nausea, bile vomits, heart burn and early dumping approximately twice as high as in our series. Differences may be due to the thoroughness of asking patients the questions but also to the length of follow-up, since Meurling (89) found a decrease of the severity of postcibal symptoms with increasing length of follow-up. Women are reported to get symptoms more often than men after gastric surgery (47, 85). We can, however, not confirm these findings as significantly less women than expected came for screening and a selection of patients with symptoms cannot be ruled out (IV).

The analysis of symptoms and gastroscopical findings may be biased. The same surgeon questioned the patient and performed the gastroscopy. The occurrence of symptoms may have influenced the grading of ERG. The limitation of ERG consists of a combination of different observations. The value of each observed parameter may have changed as more experience was gained. This may have contributed to the finding that postprandial fullness and pain correlated well to the degree of ERG but not to the degree of different histological changes in biopsies.

Nevertheless the degree of ERG was found to correlate with the scores for all different histological parameters (see VI).

A correlation between symptoms and gastroscopically observed hyperemia has been shown by Keighley et al (71). They could, however, not find any differences in the degree of acute and chronic gastritis in biopsies between patients with and without symptoms. According to our data this could be expected if the majority of symptomatic patients had postprandial pain or nausea where a correlation to histological findings was not apparent. Patients with postprandial nausea and bile vomits had significantly more ERG as well as higher scores for CAG and API. This may indicate that these symptoms are provoked by the endoscopic and histological changes found in the gastric remnant.

It cannot be ruled out that some of the patients with bile-stained vomits actually had a chronic afferent loop syndrome. It is, however, less probable that many of the patients had that etiology of their symptoms, since we would then expect a normal distribution of scores in the different histological changes in biopsies from the gastric remnant. In fact, seven patients with severe symptoms of bile vomits, postprandial nausea, fullness and pain have been reoperated. The gastroenterostomy was resected and converted to a Roux-en-Y anastomoses. In none of the surgical reports was a chronic afferent loop syndrome suspected as the etiology of the patients' symptoms. The majority of Billroth II-resections in our series had been performed retrocholically with a short afferent limb. Dahlgren (26) have shown that the incidence of the chronic afferent loop syndrome differs considerably after different Billroth II modifications and is low after retrocholic gastroenterostomies. It may therefore be important to study the original surgical report when analysing the etiology of bile vomits.

Postprandial nausea and bile vomits seem to be good selection criterion for gastroscopy and biopsy not only in order to explain the symptoms but also to detect severe atypia and early gastric cancer. Postprandial nausea and bile vomits dominated the patients' symptomatology in three patients out of seven where an early gastric cancer was diagnosed. Alterations of symptoms during follow-up have been reported to be rare and an important sign of a malignant degeneration of the gastric mucosa (39, 108, 148). In this series the symptoms as well as the duration were registered. Thus, we cannot analyse alterations of symptoms. From the symptomatic patients 80 % had experienced their symptoms since the operation. It seems therefore appropriate to suggest that patients with postgastrectomy symptoms develop more severe CAG, IM and API during follow-up. Discontent patients seem to have several reasons for being so.

In conclusion, our findings support the concept that the syndrome of postoperative reflux gastritis suggested by van Herden (145) can be looked upon as a clinical entity with good correlations between the postprandial symptoms nausea, fullness, and pain and bile vomits, and

the endoscopic picture of bile reflux, yellowish zones in close relation to the anastomosis and a thin, rigid, fragile and easily bleeding mucosa.

VI. CORRELATIONS BETWEEN GASTROSCOPIC AND HISTOLOGICAL FINDINGS IN BIOPSIES TAKEN 12 TO 49 YEARS AFTER SURGERY FOR BENIGN GASTRODUODENAL DISEASE.

SUMMARY

In 1972/1973 a series of 357 patients, previously operated on for benign gastroduodenal disease, underwent gastroscopic screening in order to detect asymptomatic gastric cancer. All examinations were performed by one endoscopist, who classified the degree of endoscopic reflux gastritis (ERG) in arbitrary units. In 1978/1979 142 patients of the original series underwent a second screening by another endoscopist, who evaluated and separately classified, the individual gastroscopic characteristics of the ERG, e.g. the degree of bile admixture, the atrophic appearance of the mucosa, the redness of the mucosa, and the occurrence of yellowish zones in close relation to the anastomosis. On both occasions biopsies were taken. These were examined by one pathologist, without any knowledge of the endoscopic findings. The degree of histological changes such as acute gastritis (AG), chronic gastritis with atrophy (CAG), chronic gastritis without atrophy (CG), chronic hyperplastic gastritis (CHG), intestinal metaplasia (IM) and atypia (API), was assessed and classified in arbitrary units.

In the 1972/1973 series, a good correlation was found between the degree of ERG and the severity of histological changes, especially CAG, IM and API. In the 1978/1979 series, bile admixture and the occurrence of yellowish zones showed the best correlation to the histological findings.

Thus, it seems that ERG diagnosed according to the degree of bile admixture and the occurrence of yellowish zones in close relation to the anastomosis has a histological counterpart, characterized mainly by CAG, IM and API. The investigation further demonstrates the necessity of a thorough evaluation of the endoscopic findings in the selection of patients where biopsies can be expected to give further useful information. The taking of biopsies from macroscopically "normal" mucosa is a waste of time and money.

The gastroscopic picture of the previously operated stomach has been described in terms of congestion or hyperemia, atrophic appearance and easy-bleeding mucosa, erosions and reflux of bile (19.71. 145). Few have analysed the picture in relation to different histological changes. Some discouraging results about the correlation between the degree of hyperemia and congestion (23, 71) and chronic gastritis may have contributed to the fact that many investigators only report data on histological changes found in biopsies, although it is well known that these biopsies are difficult specimens subject to both intra- and interindividual variation in interpretation (52, 98).

In studies on the operated stomach, the endoscopic findings are generally less thoroughly described. If easy detectable gastroscopic findings can be used to select patients with precancerous lesions and early gastric cancer, resources could be channeled to more important tasks than diagnosing chronic gastritis or confirming the presence of normal or near normal mucosa. The present study was performed in order to investigate if endoscopic reflux gastritis has a counterpart in the severity of histological findings and, if so, to evaluate the different characteristics included in the concept of endoscopic reflux gastritis.

MATERIAL AND METHODS

1. The series

In 1972/1973, 357 patients operated on for benign gastroduodenal disease 12-42 years previously were screened for gastric cancer with gastroscopy and biopsy. Four patients were found to have advanced gastric cancer and were excluded, leaving 353 for analysis. The series has been described in detail in IV.

2. Gastroscopy 1972/1973

All examinations were performed by BH with an Olympus gastroscope type EF. Patients were premedicated with 0.5 mg atropine i.m. and topical anesthesia (Xylocain[®]) of the pharynx 10 min and immediately prior to the examination, respectively. During gastroscopy, five grades of endoscopic reflux gastritis (ERG) were registered. Observations and definitions see IV.

3. Gastroscopy 1978/1979

All gastroscopies were performed by the same endoscopist (SE) with Olympus gastroscope GIF-K or GIF-B2. Patients were given a pre-medication of 15 mg propantheline bromide (Ercotina[®]) i.v. and topical anaesthesia (Xylocain[®]) of the pharynx and dimeticon (Minifom[®]) perorally immediately prior to the examination, which was performed with the patient recumbent on the left side. Findings were registered prospectively and independently of each other in four arbitrary grades (0-3). A normal finding was graded 0 and severe changes 3. The

following findings were graded:

Admixture of green bile in gastric secretion: the observation was done when the gastroscope entered the stomach. Grade 1 = slightly gray-green-stained gastric secretion. Grade 2 = green-stained gastric secretion. Grade 3 = dark green-stained gastric secretion.

The atrophic appearance of the gastric mucosa: grade 1 = thin mucosa in the fundus, otherwise normal, grade 2 = thin mucosa in the major part and grade 3 = thin mucosa in the entire gastric remnant.

Reddening of the gastric mucosa. Grade 1 = patchy reddening on the top of the gastric folds or slight diffuse reddening. Grade 2 = reddening around the anastomosis most pronounced on the major curvature. Grade 3 = pronounced reddening around the entire anastomosis.

Yellowish zones in close relation to the anastomosis; grade 1 = single grey-yellowish spots. Grade 2 = a number of spots or small continuous zones. Grade 3 = continuous zones or areas covering more than one third of the circumference of the anastomosis.

Invagination of the jejunum into the gastric remnant. This was tested by insufflating and exsufflating air in the gastric remnant. Grade 0 = an anastomosis that closes when exsufflating air. Grade 1 = a tip of the afferent loop invaginates into the gastric remnant when exsufflating air. Grade 2 = half of the afferent loop invaginates. Grade 3 = major parts of the jejunum near the anastomosis invaginate into the gastric remnant when exsufflating air.

Other findings registered separately were oesophagitis, lipid islands, erosions, polyps, cancer, jejunitis and peptic ulcers. At least 68 biopsies were taken from the gastric mucosa around the anastomosis irrespective of gastroscopic findings.

4. Histology

All biopsies were handled in a uniform manner, and interpreted by the same pathologist (EH) twice without knowledge of clinical data or endoscopic findings or the result of preceding histological examinations. The following six different histological changes were registered independent of each other: acute gastritis (AG), chronic gastritis without atrophy (CG), chronic gastritis with atrophy (CAG), chronic hyperplastic gastritis (CHG), intestinal metaplasia (IM) and atypia (API). For definitions see V. Each parameter was graded in arbitrary units 0-3, where 0 was equal to normal finding and 3 severe changes. In this study the two scores for the histological parameters in corresponding biopsies have been summed up resulting in the scores for each histological parameter to vary between 0 and 6.

RESULTS

In the 1972/1973 series a correlation ($p < 0.01 - p < 0.001$) was found between the degree of ERG and the degree of all six studied histological parameters seen in biopsies (Table I).

TABLE I

CORRELATIONS BETWEEN THE DEGREE OF ENDOSCOPIC REFLUX GASTRITIS (ERG) AND HISTOLOGICAL CHANGES IN BIOPSIES

	AG	CG	CAG	CHG	IM	API
ERG	p <0.01	p <0.01	p <0.001	p <0.001	p <0.001	p <0.001

N = 353, for AG and CG, an inverse and for CAG, CHG, IM and API a direct relation. χ^2 analysis in contiguous tables with 24 degrees of freedom.

The relation between ERG and AG or CG was found to be the reverse e.g. with increasing degree of ERG the scores for AG and CG decreased. A direct relation was found between increasing degrees of ERG and increasing scores for CAG, CHG, IM and API. The best correlation was found between ERG and API (Table II).

TABLE II

CORRELATION BETWEEN THE DEGREE OF ENDOSCOPIC REFLUX GASTRITIS (ERG) AND ATYPIA IN BIOPSIES

	ERG	0	1	2	3	4	
ATYPIA	6	0	0	1	2	1	4
	5	0	0	0	3	0	3
	4	0	2	1	5	3	11
	3	0	2	5	10	3	20
	2	5	27	41	37	7	117
	1	12	42	48	7	3	112
	0	11	33	35	6	1	86
		28	106	131	70	18	353

(N = 353, $\chi^2 = 102$, $p < 0.001$)

If we, in that table, exclude three patients with peptic ulcer and 15 with polyps (where biopsies always should be taken) we found the probability of having moderate to severe atypia or early gastric cancer (API 4-6) when a pronounced endoscopic reflux gastritis was found (ERG 3-4) to be 17 % (13 out of 76). The probability of lacking or having mild API (0-3) when endoscopic reflux gastritis was at the most mild (ERG 0-2) was 99 % (256 out of 259). The three "falsely negative" patients have been followed up and are all living without cancer after 6-7 years.

The correlations between ERG and CAG, IM and API are illustrated in Figure 9. For each degree of ERG the range for 90 % of the scores for CAG, IM and API has been shadowed and the regression line for the observations calculated.

Figures 1-4. Minor curvature always towards top of the picture. Billroth II-resected stomachs.

Fig 1. The mucosa shows slight diffuse reddening. No signs of bile reflux. Picture is taken during exsufflation of air when the anastomosis closes. A typical lipid island is seen.

Fig 2. Congested and reddened mucosa. Afferent loop invaginated into the upper part of the anastomosis. A jet of bile is seen to hit the major curvature.

Fig 3. Distinct yellowish zone on the borderline between the reddened gastric and the pale jejunal mucosa. A lipid island is seen in the right upper part of the picture.

Fig 4. Large invaginated stoma with ample reflux of bile. Yellowish zone in close relation to the minor side of the anastomosis. Along the major curvature markedly reddened mucosa with small grey spots.

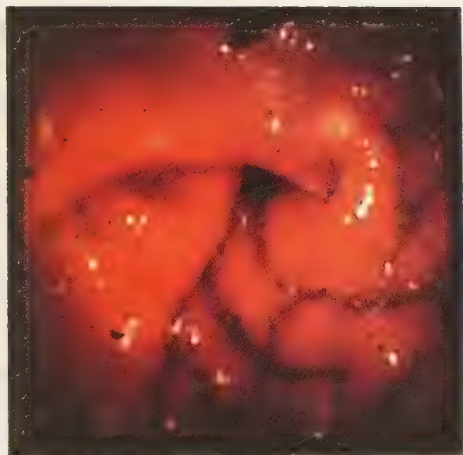


Figure 1

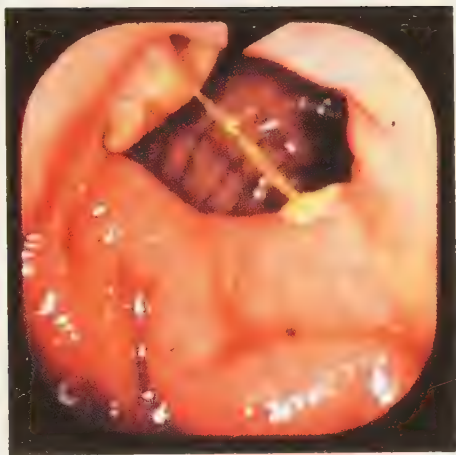


Figure 2

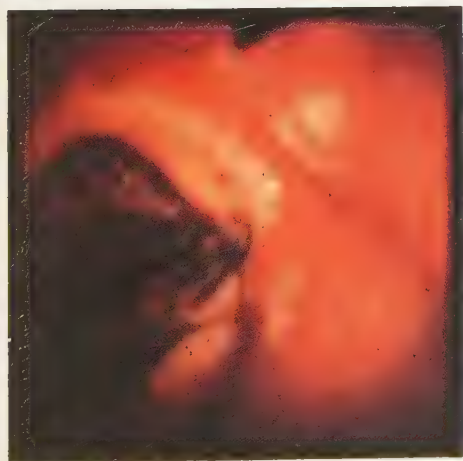


Figure 3



Figure 4

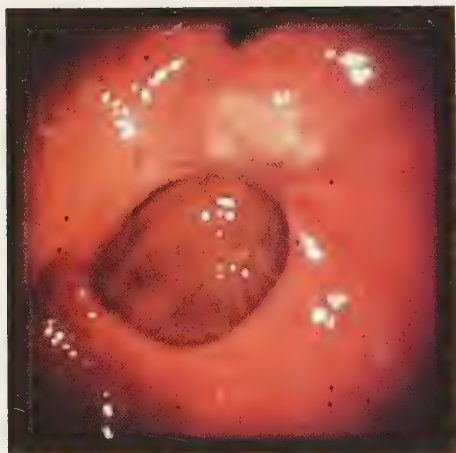


Figure 5

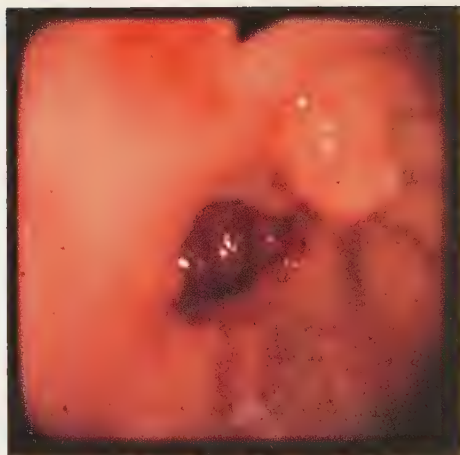


Figure 6



Figure 7

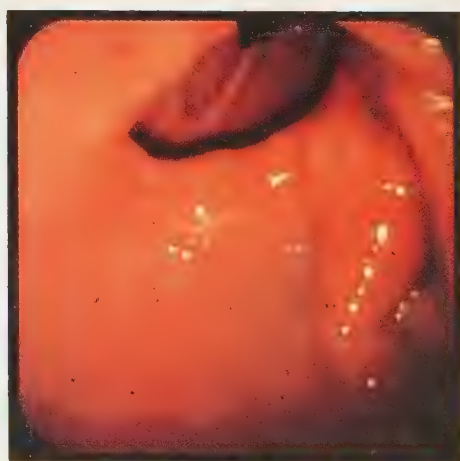


Figure 8

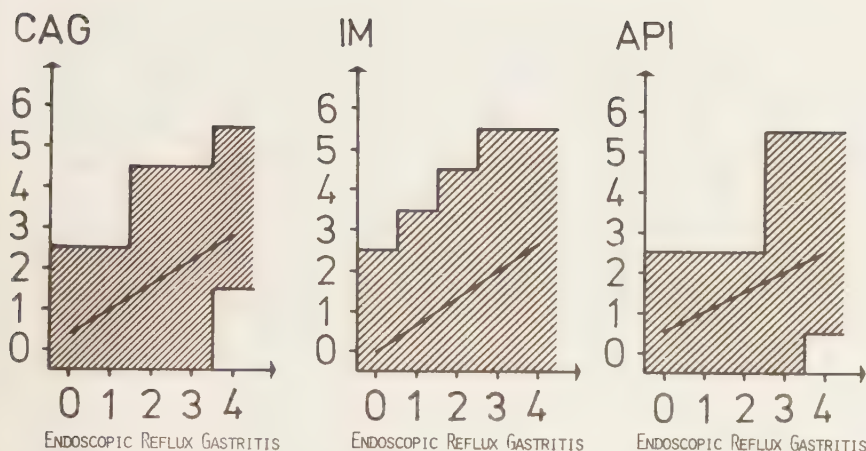


Fig 9. The relation between the degree of endoscopic reflux gastritis (ERG) and chronic atrophic gastritis (CAG), intestinal metaplasia (IM) and atypia (API) in biopsies. Ninety per cent of column cell frequencies within the shadowed areas. Straight line indicates the regression line for the observations.

Figures 5-8. Minor curvature always towards top of the picture.

Fig 5. The mucosa looks thin and rigid. Near the anastomosis on the minor curvature a small but typical advanced cancer is apparent. The tumor is ulcerated on the top and infiltrates underneath the adjacent mucosa.

Fig 6. Patient re-resected and converted to Roux-en-Y for an early gastric cancer close to a Billroth II-anastomosis, two years prior to the examination. Pale mucosa without signs of bile reflux. Two cm from the anastomosis on the minor curvature a small polyp is seen. Biopsy confirmed a recurrence of early cancer.

Fig 7. Severe endoscopic reflux gastritis with thin, rigid and easily bleeding mucosa. Reddening but no congestion along the major curvature. The polyp seen in the upper part of the picture was benign. Biopsy around the anastomosis showed an early gastric cancer with an upper boundary identical with the borderline between reddened and pale gastric mucosa.

Fig 8. Moderate atrophic appearance of the mucosa. A swollen fold is seen radiating towards the anastomosis. On the top of the fold a 1 cm large erosion is apparent. Biopsy showed early gastric cancer.

The correlations between gastroscopic and histological findings in the 1978/1979 study are presented in Table III. The atrophic appearance of the gastric mucosa seen at gastroscopy did not correlate significantly with CAG in biopsies taken around the anastomosis. The degree of redness of the gastric mucosa correlated ($p < 0.05$) with the degree of CAG and API. The single observation that discriminated the scores of studied histological parameters best was grey-yellowish zones in close relation to the anastomosis. The correlations with CAG, IM and API were highly significant ($p < 0.001$) (Table IV). The bile admixture in the gastric secretion correlated well with CAG, CHG and IM but best with API ($p < 0.001$). Six out of 11 patients with dark green-stained gastric secretion had moderate to severe atypia (API 4-6) in biopsies taken around the anastomosis.

TABLE III

CORRELATIONS BETWEEN THE DEGREE OF DIFFERENT GASTROSCOPIC AND HISTOLOGICAL FINDINGS

1978/79	AG	CG	CAG	CHG	IM	API
Atrophic appearance of mucosa	NS	NS	NS	NS	$p < 0.05$	NS
Redness of anastomosis	NS	NS	$p < 0.05$	NS	NS	$p < 0.05$
Yellowish zones in the anastomosis	NS	$p < 0.05$	$p < 0.001$	NS	$p < 0.001$	$p < 0.001$
Bile admixture	NS	$p < 0.05$	$p < 0.01$	$p < 0.01$	$p < 0.05$	$p < 0.001$
Invagination of afferent loop	NS	$p < 0.05$	$p < 0.001$	$p < 0.01$	$p < 0.05$	NS

N = 142. For AG and CG an inverse and for CAG, CHG, IM and API a direct relation. χ^2 analysis in contiguous tables with 16 degrees of freedom. NS = not significant.

TABLE IV

CORRELATION BETWEEN THE DEGREE OF YELLOWISH ZONES
AROUND THE ANASTOMOSIS AND THE DEGREE OF ATYPIA IN
BIOPSIES

		YELLOWISH ZONES				
		0	1	2	3	
ATYPIA	6	0	0	0	1	1
	5	0	0	2	0	2
	4	4	2	6	5	17
	3	4	3	4	0	11
	2	18	18	7	7	50
	1	14	2	1	1	18
	0	28	9	5	1	43
		68	34	25	15	142

$N = 142$, ($\text{Chi}^2 = 42$, $p < 0.001$)

The degree of bile admixture correlated well ($p < 0.001$) with the degree of invagination of the jejunal mucosa into the gastric remnant (Table V) and the latter also correlated with the degree of CAG ($p < 0.001$), CHG ($p < 0.01$) and IM ($p < 0.05$).

Table V. Degree of afferent loop invagination and bile admixture to gastric secretion.

		Bile admixture				Total
		0	1	2	3	
Invagination of afferent loop	3	0	2	1	1	4
	2	2	16	30	8	56
	1	2	19	8	0	29
	0	16	27	8	2	53
Total		19	64	47	11	142

($N = 142$, $\text{Chi}^2 = 43$, $p < 0.001$)

The correlations between bile admixture yellowish zones around the anastomosis and some histological observations in biopsies are illustrated in Figure 10.

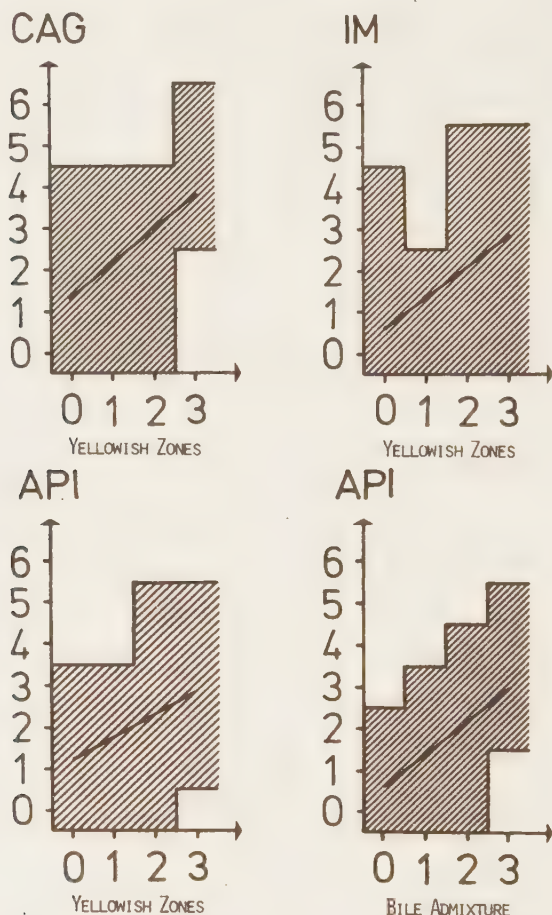


Fig 10. Relation between the degree of yellowish zones or bile admixture and chronic atrophic gastritis (CAG), intestinal metaplasia (IM) and atypia (API) in biopsies. Ninety per cent of column cell frequencies within shadowed areas. Straight line represents the regression line for the observations.

DISCUSSION

The general clinical experience is that the the operated stomach shows a typical gastroscopic picture. Some have not been able to find a correlation between gastroscopic and histological changes (23, 71) and others recommend biopsies in all cases, as the diagnosis of early gastric cancer (EGC) in most cases comes as a surprise (125). In our experience most EGC:s were accompanied by severe endoscopic changes. We found one EGC (of the diffuse type according to Laurén classification) in an apparently normal gastric remnant in approximately 700 examinations. Our findings do not support the recommendations of mandatory routine biopsies. We recommend that the selection criteria for taking biopsies should be tumors, ulcerations, erosions and pronounced endoscopic reflux gastritis. In the first screening 1972/1973 the number of biopsies could have been reduced from 357 to 99, or by 72 %, without any obvious negative effects.

When analysing the individual characteristics included in the concept of ERG we could not find that the atrophic appearance of the gastric mucosa correlated with CAG in biopsies. Stadmann (133) reports an increasing degree of histological atrophy from the fornix towards the anastomosis. Biopsies taken from the anastomosis thus ought to express the highest degree of atrophy. The simultaneous occurrence of hyperemia and congestion may explain the difficulties in correlating endoscopic and histological atrophy.

Hyperemia, or reddening of the mucosa around the anastomosis have been considered important endoscopic signs of an altered gastric mucosa. We found a correlation with the degree of CAG and API but only on the 5 % level. The presence of hyperemia is, however, probably necessary for detecting the grey-yellowish zones in close relation to the anastomosis. These are seldom observed in patients where reddening is rare e.g. in patients that have a Roux-en-Y anastomosis (43). The occurrence of yellowish zones are easy to distinguish from lipid islands (34, 139). Yellowish zones are always situated on the borderline between gastric and jejunal mucosa. In pronounced cases the zones grow wider and in the adjacent often reddened mucosa multiple grey small spots are seen. These zones were originally believed to represent intestinal metaplasia since the colour corresponded well to that of the adjacent jejunal mucosa. No separate investigation was performed in order to verify this. Therefore the results cannot be used to identify the true nature of yellowish zones. Nevertheless, these macroscopic changes are important both for the identification of the concept of ERG and for the selection of patients where biopsies can be expected to exhibit important histological changes. However, the best correlation between endoscopic and histological changes was found for the concept of ERG and not for the individual characteristics. In the most severe degree of ERG the thin, rigid, mucosa is a dominating finding.

Hammar (52) showed that precancerous changes were most severe close to the efferent limb in a Billroth II-anastomosis. The standard procedure during the period patients in this series were operated was the Hofmeister-Finsterer modification (e.g. retrocolic gastroenteroanastomosis with the afferent limb sutured to the minor side of the stomach). Hammar suggested that the opposite side of the afferent limb in the gastric remnant was maximally exposed to bile reflux. When looking at a case with invagination the afferent loop actually invaginates towards the area where Hammar found the most severe histological changes (Fig 2). Invagination seems, however, not to be a necessary finding for the reflux of bile since bile admixture in the gastric secretion was found to be more sensitive in discriminating patients with severe histological changes.

Borg (9) examined fasting gastric aspirates after Billroth II-resections and found 25 % to be unstained, 16 % slightly stained and 59 % bile-stained. Although gastroscopy is a more unphysiological examination than to pass down a nasogastric tube our findings correspond fairly well to Borgs. As we found good correlation between bile admixture and the degree of CAG, IM and API in biopsies, a gastroscopy with biopsy could be recommended if gastric aspirates (e.g. collected at a secretion test) are found to be heavily bile-stained.

In conclusion, the present study demonstrates that a thorough evaluation of the gastroscopic picture of the operated stomach can select patients where biopsies may give further information from those where the histological findings will not change further clinical management.

VII. CAN GASTROSCOPIC OR MICROSCOPIC FINDINGS IN BIOPSIES BE USED TO PREDICT THE DEVELOPMENT OF GASTRIC CANCER IN THE OPERATED STOMACH?

SUMMARY

A series of 357 patients operated on for benign gastroduodenal disease 12 to 42 years previously were screened for gastric cancer in 1972/1973 with gastroscopy and four routine biopsies around the anastomosis. One endoscopist classified and graded the endoscopic reflux gastritis. The biopsies were classified and graded by one pathologist. In 346 patients no cancer was found. During follow-up, until October 1st 1979, 3 advanced and 8 early gastric cancers were diagnosed. The degree of endoscopic reflux gastritis did not differ between those patients who developed cancer during the follow-up and those who did not. Patients who developed cancer had a higher degree of chronic atrophic gastritis, chronic hyperplastic gastritis and possibly also atypia in the initial biopsies.

Thus, in the resected stomach chronic atrophic gastritis, chronic hyperplastic gastritis and atypia can be regarded as precancerous lesions associated with an increased risk of developing cancer. However, for the individual patient the finding of gastritis and/or atypia in biopsies is a weak predictor for the development of cancer during six to seven years follow-up since the majority of patients with severe histological changes did not develop cancer.

Patients with an operated stomach have an increased risk of dying of gastric cancer when the time period after the operation exceeds 15 years (11, 35, 55). Thus, the operated stomach may be regarded as a precancerous condition. Morphologically, a precancerous lesion is defined as a histopathological abnormality in which cancer is more likely to occur when compared to its apparently normal counterpart (97). Chronic atrophic gastritis, intestinal metaplasia and atypia have been considered precancerous lesions (51, 68, 70, 92, 96, 99, 100, 115, 130) and are commonly seen in biopsies from the operated stomach (32, 33, 123, 125). However, these lesions do not inevitably develop into cancer but could be regarded as markers of an increased probability, or risk, of developing cancer. The magnitude of such a risk has not been established (97).

If some macro- or microscopic findings could be shown to be associated with an increased risk of developing cancer, routines could be established to detect cancer at an early stage by close surveillance of these patients with gastroscopy and routine biopsy.

The aim of this study was to investigate if endoscopic reflux gastritis or the degree of different histological changes found in biopsies differed between those patients who later developed cancer and those who did not.

MATERIAL AND METHODS

1. The series

In 1972/1973 357 patients initially operated on for benign gastroduodenal disease with a resection or gastroenterostomy alone were screened for gastric cancer with gastroscopy and biopsy after a time interval of 12-42 years. Four advanced and seven early cancers were diagnosed and these patients have been excluded. After the initial examination follow-up was planned according to clinical praxis, e.g. patients with severe atypia in biopsies were after an initial re-examination followed at yearly intervals with a new examination. Severe atypia has not been accepted as an indication for surgery at the Department of Surgery in Lund, but has contributed to the indication for a reoperation of one patient.

During the last part of 1978 and first part of 1979 patients were offered a new screening. Death certificates were collected until October 1, 1979. Out of 57 deceased patients one had an advanced cancer that was not diagnosed prior to death and one had been operated for early cancer three years earlier. Hospital records were during the same time collected from 122 patients that did not attend the second screening. During the follow-up period 11 patients had developed gastric cancer, three being advanced and eight early. Patients that did not develop cancer were divided into three different groups that, with different degrees of certainty, had not developed cancer. Group 1 consists of 151 patients that went through

the second screening in 1978/1979 with gastroscopy and biopsies and thereafter were judged free from cancer. Group 2 consists of an additional seven patients that, in between the two screening procedures, were reoperated because of severe symptoms of reflux gastritis and converted to Roux-en-Y where neither the operative specimens nor gastroscopy and biopsies during follow-up showed signs of cancer. The third group consists of all those 335 patients that to our knowledge did not develop cancer.

2. Gastroscopy

The screening in 1972/1973 was performed by one endoscopist (BH) who graded the degree of endoscopic reflux gastritis (ERG) in arbitrary units (0-4), zero implying normal gastric mucosa and 4 severe changes. For definitions see V. At least four biopsies were taken routinely on the gastric side around the anastomosis.

The second screening in 1978/1979 was performed by one endoscopist (SE) and 6-8 biopsies were taken routinely around the anastomosis. If severe atypia was found in biopsies or the gastroscopic lesion gave suspicion of cancer the gastroscopy was repeated before the patient was judged free from cancer.

3. Histology

All biopsies were handled in a uniform manner and investigated by one pathologist (EH) who characterized and graded different histological findings independent of each other in arbitrary units (0-3) where 0 was normal and 3 severe changes. The biopsies were graded twice without knowledge of clinical, gastroscopic or preceding histological data. The following histological changes were graded: acute gastritis (AG), chronic gastritis without atrophy (CG), chronic gastritis with atrophy (CAG), chronic hyperplastic gastritis (CHG), intestinal metaplasia (IM) and atypia (API). For definitions see V. The scores for corresponding histological parameters and patients in the two investigations have been summed up. Each histological parameter thus gets a score varying from 0 to 6. For API the range is 0-4 since patients scoring 5 or 6 at the initial examination all had gastric cancer and were excluded.

4. Statistical methods

The Mann-Whitney u-test was used to test differences between groups.

RESULTS

In Table I the number of patients with different degrees of ERG among those who developed cancer and among patients in the three different groups that did not is shown. No statistical difference was found concerning the risk of later development of cancer in the three groups with different grades of ERG.

TABLE I

SEVERITY OF ENDOSCOPIC REFLUX GASTRITIS (ERG) AT THE INITIAL EXAMINATION. FOLLOW-UP 6-7 YEARS.

ERG SCORES 1972/73		0	1	2	3	4	
Cancer during follow-up	n = 11	-	4 **	3	4 *	-	NS
Group 1	n = 151	10	47	50	33	11	NS
Group 2	n = 158	11	47	52	35	13	NS
Group 3	n = 335	28	102	127	61	17	
Total	n = 346	28	106	130	65	17	

* indicates each patient developing advanced gastric cancer during follow-up.

Patients who developed cancer during follow-up had significantly more severe CAG and CHG in biopsies 1972/1973 than the patients who did not develop cancer ($p < 0.05$). No differences could be detected for the degree of AG, CG, and IM. Patients that developed cancer had a more severe degree of API but the differences did not reach the commonly accepted levels of statistical significance (against group 1, $p = 0.057$, group 2, $p = 0.075$ and group 3, $p = 0.055$) (Table II).

In Fig 1 the quotient between the observed and expected ratios of detected cancers is shown for patients with different degrees of histological changes. The expected ratio has been calculated with the assumption that all degrees of histological changes were associated with the same risk of developing cancer. For patients without CAG the risk during follow-up was approximately half the expected and for patients with severe CAG the risk increased three to five times. Patients with severe IM seem to run a 3- to 5-fold increased risk. Patients without API in biopsies could be expected to have half the average risk and those with moderate API two to three times the expected risk of developing cancer during a six to seven year follow-up.

TABLE II

SEVERITY OF HISTOLOGICAL CHANGES IN BIOPSIES AMONG PATIENTS WHO DEVELOPED CANCER AND WHO DID NOT. FOLLOW-UP 6-7 YEARS.

AG scores in biopsies 1972/73

Cancer during follow-up	n	0	1	2	3	4	5	6
Group 1	n = 11	-	-	3*	2	5*	1*	-
Group 2	n = 151	17	18	20	28	59	6	3
Group 3	n = 158	17	19	21	29	63	6	3
Group 3	n = 335	29	40	50	53	137	20	6
Total	n = 346	29	40	53	55	142	21	6

NS

NS

NS

CHG scores in biopsies 1972/73

Cancer during follow-up	n	0	1	2	3	4	5	6
Group 1	n = 11	-	-	-	1	5*	2*	3*
Group 2	n = 151	-	5	12	33	77	23	1
Group 3	n = 158	-	5	13	33	82	24	1
Group 3	n = 335	1	5	35	62	183	44	5
Total	n = 346	1	5	35	63	188	46	8

p<0.05

p<0.05

p<0.05

CG scores in biopsies 1972/73

Cancer during follow-up	n	0	1	2	3	4	5	6
Group 1	n = 11	5	-	2*	3*	-	-	1*
Group 2	n = 151	34	11	39	24	35	7	1
Group 3	n = 158	37	11	41	24	37	7	1
Group 3	n = 335	68	20	97	51	85	11	3
Total	n = 346	73	20	99	54	85	11	4

NS

NS

NS

IM scores in biopsies 1972/73

Cancer during follow-up	n	0	1	2	3	4	5	6
Group 1	n = 11	6**	1	-	-	1	1	2*
Group 2	n = 151	86	6	17	8	23	8	3
Group 3	n = 158	89	6	17	9	26	8	3
Group 3	n = 335	198	26	39	15	41	12	4
Total	n = 346	204	27	39	15	42	13	6

NS

NS

NS

CAG scores in biopsies 1972/73

Cancer during follow-up	n	0	1	2	3	4	5	6
Group 1	n = 11	3**	-	2*	1	3	2	-
Group 2	n = 151	75	6	36	12	15	4	3
Group 3	n = 158	77	7	37	12	17	4	4
Group 3	n = 335	162	15	94	17	36	7	4
Total	n = 346	165	15	96	18	39	9	4

p<0.05

p<0.05

p<0.05

API scores in biopsies 1972/73

Cancer during follow-up	n	0	1	2	3	4
Group 1	n = 11	2*	1	5	2**	1
Group 2	n = 151	54	35	44	11	7
Group 3	n = 158	54	37	46	13	8
Group 3	n = 335	84	111	112	18	10
Total	n = 346	86	112	117	20	11

p = 0.057 NS

p = 0.075 NS

p = 0.055 NS

* indicates each patient developing Advanced Gastric Cancer during follow-up.

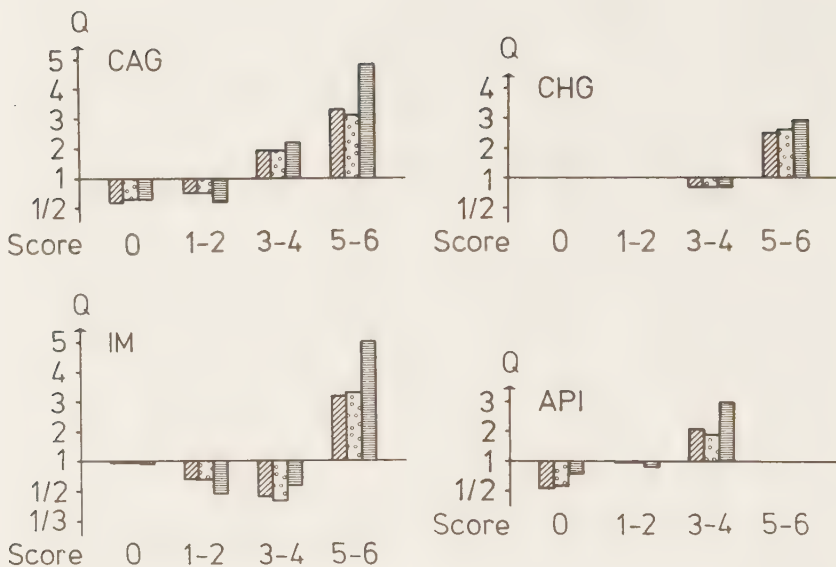


Fig 1. Quotient (Q) between observed and expected risk of developing cancer during six to seven years follow-up, for patients with different degrees of histological changes in biopsies taken at the initial examination 1972/1973. CAG = chronic atrophic gastritis, CHG = chronic hyperplastic gastritis, IM = intestinal metaplasia, API = atypia. ▨ = group 1 (n = 151), ▩ = group 2 (n = 158), ■ = group 3 (n = 335).

DISCUSSION

The follow-up rate among patients with both severe ERG and histological changes has been higher than among those with more discrete findings. The patients' interpretation of the endoscopists response to results of earlier examinations has probably been influenced by the endoscopists' opinion that severe changes ought to be checked. Groups 1 and 2 are thus biased, meaning that if patients who developed cancer after the initial examination actually had higher scores differences are more difficult to detect. Group 3 is in this respect less biased but the patients are also less well examined. Since all patients got an invitation for screening and hospital records have been reviewed it is, however, unlikely that they had a symptomatic gastric cancer.

During seven years follow-up the degree of ERG at the initial examination gives no guidance for recommending a specific time interval for re-examination. There are no suggestions that the gastroscopic picture could discriminate patients prone to develop gastric cancer but the clinical practice has often been to re-examine patients with severe gastroscopic changes more often. A good correlation between the degree of ERG and the degree of histological changes such as CAG, IM and API has been reported earlier (VI). However, the necessary prerequisite for such a correlation seems to be an atrophy of the gastric mucosa (43). Patients who developed cancer had, as a group, significantly more pronounced CAG at the initial examination. The differences in degree of atrophy were probably not large enough to influence the degree of ERG.

The precancerous nature of CAG has been established in clinical follow-up studies in two non-operated populations. In a prospective study of 116 patients with atrophic gastritis followed 19-23 years Siurala et al (131) found 10 gastric cancers whereas one had developed in a control group with normal mucosa or superficial gastritis only. Our follow-up time is much shorter but even in the first report five to eight years after the diagnosis of atrophic gastritis Siurala et al (129) found a considerable number (6/116) of patients with gastric cancer. Comparable results have been reported by Walker et al (142) who found four cancers after a mean follow-up period of 15 years of 40 patients. In patients with CAG the annual incidence of advanced cancer during follow-up could, in Siurala's series, be estimated to be approximately 0.4 %. In this series only one advanced cancer developed from a population of 181 patients with some degree of CAG during six to seven years follow-up. We have to assume that four patients operated on for EGC, if not operated, would have developed AGC during the follow-up period if we are to obtain the same annual incidence as in Siurala's series. This raises expectations of future possibilities to detect an effect of early gastric cancer treatment on cancer mortality.

Both advanced and early gastric cancers are surrounded by IM in high frequencies (66, 96, 115). In Siurala's et al series seven out of nine cancers developed in stomachs with CAG combined with IM. Among our resected patients no significant correlation between the degree of IM in biopsies 1972/1973 and the risk of developing cancer during follow-up could be detected. Only patients with the most severe degree of IM seem to run an increased risk. However, as the distribution of IM is patchy we might have taken too few biopsies to detect a true correlation. The incidence of IM, irrespective of degree, in our series was 40 %. Domellöf et al (32, 33) took six biopsies and report an incidence of 33-40 %. Although Schrupf et al (125) usually took 20 biopsies they report a lower incidence of IM (22-25 %). This does not mean that we recommend only four biopsies. Today when biopsy is indicated eight to ten is the routine. However, it seems unlikely that the majority of patients in our series where no IM could be detected actually have had a metaplastic mucosa.

Correra et al (22) studied in biopsies from one gastric cancer high risk and one low risk population, the probability of transition from normal gastric mucosa to superficial gastritis and from superficial gastritis to CAG without IM and from CAG without IM to CAG with IM, with the assumption that this was the evolution of gastritis before gastric cancer developed. The greatest differences between studied populations were found in the risk of advancing from normal mucosa to superficial gastritis and from superficial gastritis to CAG without IM. The rate of transition from CAG without IM to CAG with IM did not differ between the studied populations. Correra et al remark that IM may merely represent a continuation of the atrophic process per se. Our data does not contradict this statement. Only severe IM could be correlated to an increased risk of developing cancer. Surgical specimens in 10 out of 11 cancers were surrounded IM, suggesting severe IM to be a late process before the stage of cancer.

Little is known about the importance of the degree of atypia or dysplasia, irrespective of the degree of other histological findings, as a marker for an increased risk of developing cancer. The distributions of severe atypia and early gastric cancer in the operated stomach have been studied by Hammar (53) who showed that the most severe changes were seen close to the anastomoses, preferably adjacent to the efferent loop. When taking biopsies around the anastomosis Schrupf et al (125) report severe dysplasia in biopsies in 3 % 20-25 years after surgery for a benign condition and moderate dysplasia in 12 %. The risk associated with dysplasia has not been established, although in several reports patients have been re-operated, probably on the assumption that the majority of patients with severe dysplasia will develop cancer (33, 123, 125). Ohlert et al (102) studied 119 patients with severe dysplasia during 1-24 months of follow-up and found that 22 % decreased in severity, 78 % were unchanged and no patient developed cancer.

In our series eight patients with an API score of 4 (API grade 2 in both examinations) were followed during seven years. The API on biopsies 1972/1973 was neither judged highly probable to be taken from a cancer nor to be reactive. With WHO terminology the lesions belonged to the group moderate or severe dysplasia (V). One patient developed cancer, three still have the same degree of API, and in four the grade of API has decreased during follow-up (Figs 2-4). As seen in Fig 1 the risk of developing cancer is related to the degree of API but risks involved are not extremely high. Patients with "borderline lesions" (API 3-4) had two to three times the average risk. The annual incidence of transition from a "borderline" lesion to cancer could be expected to be 2-3 % (three out of 21 during six to seven years). Naturally patients with this type of lesions should first of all be submitted to a thorough examination with multiple biopsies attempting to verify the true nature of the lesion and secondly be followed with repeated gastroscopy and biopsy examinations. However, if progression occurs it seems to be a slow process and our data gives no support to re-examining these patients several times a year (100). Yearly

intervals seem to be reasonable.

A weighed malignancy index taking into account all histological parameters might be of value but has the disadvantage of being complicated and not suitable for the routine situation. CHG was found to be precancerous lesions. When calculating risks an estimation of the degree is of less value since CHG is commonly seen in biopsies. Severe CAG and IM and cellular and glandular atypia are the histological changes that are not too frequently seen, relatively easy to detect and markers for an increased risk. Thus these changes could constitute the basis for the histological evaluation of the risk of developing gastric cancer in the operated stomach.

We have calculated the magnitude of risks associated with different histological changes in biopsies. In previous studies (II) risks have been calculated on the basis of clinical data such as age at and length of interval from primary surgery and the type of ulcer disease. Added risks may occasionally be considered so high, and surgical risks so low that a prophylactic operation might be considered. An increased risk, assessed from histological findings only, should, in our opinion, only lead to variation of follow-up interval where yearly intervals could be recommended in patients with severe histological changes.

Representative pair of microscopic photographs from gastric biopsies in three different patients (1972/1973 to the left and 1978/1979 to the right).

Fig 2. shows a foveolar hyperplasia as well as cellular and glandular atypia of mild to moderate degree. Six years later the degree of atypia has increased slightly. No signs of cancer (H & E x 100).

Fig 3. Moderate atrophic gastritis combined with atypia (PAS x 100). The degree of atypia is unchanged five years later but the degree of atrophy has increased. No signs of cancer (H & E x 100).

Fig 4. Moderate degree of cellular and glandular atypia and intramucosal cysts was found at the initial examination. Seven years later the severity of histological changes has decreased (H & E x 100).

Fig. 2

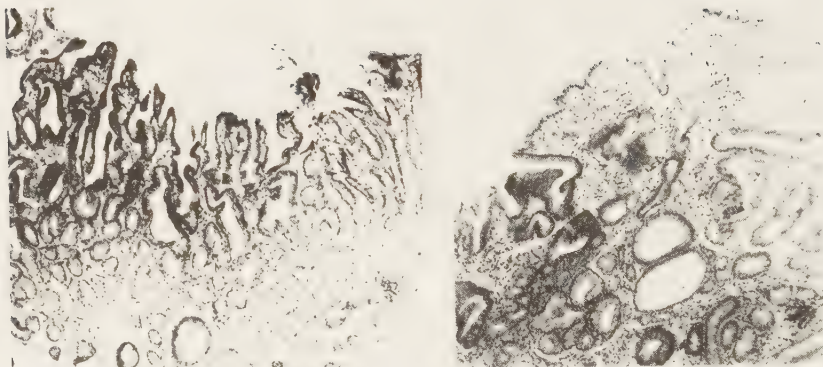
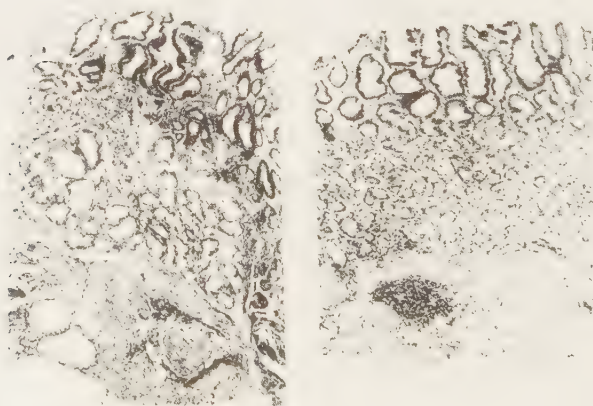


Fig. 3



Fig. 4



GENERAL SUMMARY

In order to estimate the magnitude of the risk of developing cancer in the operated stomach all patients who underwent surgery for a benign gastroduodenal disease between 1930 and 1960 at the Department of Surgery in Lund were identified from hospital files. After excluding patients who died within five years after surgery from gastric cancer, or had a vagotomy and pyloroplasty, simple closure of a perforated ulcer, local excision or simple gastrostomy performed, 1 575 patients remained. Out of these it was possible to trace 1 403. By October 1st, 1979, 763 patients had died, 21 were lost to follow-up and 619 were still alive. For deceased patients the main cause of death according to the death certificate was registered. In 28 patients gastric cancer was stated as the cause of death. Three were excluded since they were found to have already had cancer at the primary operation and one because he actually died from colonic cancer.

The expected number of deaths in a specific disease has been calculated, corrected for age and sex, from the numbers in the publication "Causes of Death", by the National Central Bureau of Statistics in Sweden. To test the method of analysis and for comparison with earlier published data 11 different diagnoses or diagnostic groups as well as the total mortality was studied.

The overall mortality rate is in accordance with that expected. However, more patients than expected died from malignant and benign pulmonary diseases, general atherosclerosis and suicide.

In 1954 the WHO system was adopted in Sweden for registration of causes of death. A less detailed classification system was used before that year. In order to study individual diagnoses we used statistics from 1957 to estimate the number of expected deaths from 1930 to 1957. The year 1957 was chosen in order to allow the new system to be generally adopted. Thus we had to assume that the death rates from 1930 to 1957 were unchanged. As age specific mortality rates probably decreased during that period, the estimated number of deaths could be somewhat too low. Only 20 % of the deaths occurred before 1957 and most of the patients were operated prior to that year.

The method of calculating the expected number of deaths is the same as that used by other investigators (17, 56, 78, 86). The use of official death statistics for calculating the expected number has obvious draw-backs. The certainty with which the different diagnoses are established, may differ between patients and the general population.

The autopsy frequency has not been analysed in this series. On the other hand, calculations of the expected number of deaths take into account the two known important factors related to the risk of dying of most diseases, e.g. age and sex. If death rates are found to be considerably higher than in the general population preventive measures could be considered.

After excluding postoperative deaths the overall mortality rate in the studied sample of patients was not different from that expected (I). This finding differs from earlier reports. Krause found significantly more deaths (210) than expected (163) in the follow-up of 361 patients 23-50 years after surgery. The diagnoses contributing to the increased mortality were tuberculosis, gastric cancer and suicide. Tuberculosis is today a rare disease also among operated patients (118). We have only registered one patient who died from that disease. If the 24 patients who were reported to have died of tuberculosis in Krause's series, were alive at follow-up the difference between observed and expected number of deaths is no longer significant. This indicates that the risk of premature death after gastric surgery may be decreasing.

Ross et al (1982) studied 799 males, divided in three age groups, 30-39, 40-49 and 50-59 years, 15-32 years after surgery. Irrespective of age at surgery an excess mortality was found compared to the general population. The shortening of life expectancy was approximately nine years. This was related to smoking associated diseases, which accounted for 200 out of 360 deaths against 171 expected. Included in smoking associated diseases were carcinoma of the lung and other respiratory sites, carcinoma of the oesophagus, chronic bronchitis, emphysema, pulmonary heart diseases and ischemic heart diseases. When studying individual diagnoses deaths from cancer of the lung was the only smoking associated disease where the observed number of deaths was significantly different from the expected. In our series we could verify that males operated on before the age of 40 ran a significantly increased risk of premature death. In this age group we found 76 deaths against the expected 52.2. All other age groups had mortality rates within the range of the expected. Unfortunately Ross et al do not give the causes of death in the different age groups to allow comparison. In the Lund series 40 % of the deaths in males operated on before the age of 40 were caused by suicide (12), lung cancer (8), gastric cancer (6) and bronchopneumonia (4) indicating a markedly different mortality pattern compared to the normal population. Such differences were not equally apparent in the older age groups. However, an excess mortality was found in some smoking associated diseases, e.g. lung cancer, bronchopneumonia and general arteriosclerosis. In the series of Ross et al 83 % were cigarette smokers at the time of operation and few ceased to smoke after surgery. Smoking habits, ulcer disease and life expectancy are all related to social background. Since the Lund series and that of Ross et al were recruited from different types of populations this may have contributed to the difference between the results.

In most surgical series more deaths than expected are caused by suicide (74, 78, 118). Our finding is thus in agreement with other investigators'. The 38 deaths from suicide were evenly distributed during the period 2-25 years after surgery in our series. In a study from Copenhagen 1 000 duodenal ulcer patients were followed up by Knop & Fischer 21-29 years after surgery. They found that 67 out of 490 (13.7 %) deaths were caused by suicide, with no correlation to the interval after the operation. Viskum studied attempted and committed suicide in 2 619 patients suffering from peptic ulcer disease. The number of patients attempting and committing suicide exceeded the expected significantly but no difference was found between operated and non-operated patients. Thus, taken together, evidence indicates that the increased risk of committing suicide is related mainly to the peptic ulcer disease and not to the operation.

In conclusion, the statistical analysis of the causes of death from different diseases yields information in accordance to what others have found. We can confirm earlier reports of the increased risk of dying of benign and malignant pulmonary diseases, general arteriosclerosis and suicide but are not able to verify that patients after peptic ulcer surgery are bad risks in life insurance terms, as stated by Ross et al, except the subgroup of patients less than 40 years of age at surgery.

During a mean follow-up period of 26 years the mortality from gastric cancer is not different from the expected.

Different opinions exist as to whether or not gastric surgery for benign gastroduodenal disease is associated with an increased risk of dying of gastric cancer (17, 35, 36, 57, 105). Autopsy studies ought to be reliable for the assessment of the risks involved. In some studies the risk is found to be twice the expected (60, 79, 134) and in others not different from that in matched controls (73). Most autopsy studies have the disadvantage of being performed at university clinics with the possibility of a biased result. Difficult cases are selected there. Cancer in the resected stomach was a difficult diagnosis prior to the modern gastroscopy era. Stalsberg & Taksdal (1971) reported that 31 % (17/55) of stump cancers had not been diagnosed prior to autopsy against 16 % (9/55) of cancers in the non-operated stomach.

Follow-up studies on clinical series using the official death statistics have the advantage of covering most operated patients but the distinct disadvantage of a less reliable basis for registration of the main cause of death. Furthermore, patients in the Lund series

still alive in 1972 were subjected to a number of measures specifically aiming at the diagnosis and treatment of gastric cancer. If these attempts have been successful, the registered number of deaths from gastric cancer in 1979 should be less than expected from an operated series of patients.

Domellöf et al (35) showed that the incidence of gastric cancer was lower than expected during the first eight years after surgery and higher after more than 12 years. The mean follow-up interval in our study was 26 years (range 19-49). A decreased risk of dying during the first eight years may balance an increased risk during the following 10-15 years, indicating that the length of follow-up in clinical studies must be long enough to detect the true increased mortality from gastric cancer. In studies with the same length of follow-up others, such as Krause and Helsing & Hillestad, found more gastric cancers than expected. In the earlier mentioned study of Ross et al as well as in the Lund series the number of deaths from gastric cancer was not different from the expected. This indicates that other risk factors may be involved besides the length of follow-up.

The probability of developing cancer in the gastric remnant has been reported to be as high as 10 % (48, 107) but the average figure is 3 % (39, 78, 118). In our series 3 % of deaths were due to gastric cancer. As patients at the end of follow-up were on the average 69 years old the probability of dying of other causes increases rapidly. At the same time the long interval from primary surgery increases the risk of dying from gastric cancer (II). Further follow-up may give an answer to the question if the overall mortality rate and the gastric cancer mortality rate will run in parallel.

Patients operated on for gastric ulcer develop cancer after a shorter time interval than patients operated on for duodenal ulcer.

A shorter interval between primary surgery and death in gastric cancer for gastric compared to duodenal ulcer patients has earlier been reported by Papachristou et al. Not much attention has otherwise been paid to the difference in length of the free interval for different ulcer diseases.

We have used the life table method of Kaplan-Meier to analyse differences in cumulative survival from gastric cancer, all other deaths being regarded as withdrawals. The life table method should be used when binominal events are studied in relation to time. Even if the number of terminal events in each time period studied were few a statistically significant difference could be detected. The results

suggest that gastric ulcer patients develop gastric cancer after a shorter time interval than duodenal ulcer patients. After 40 years differences were no longer apparent (II).

These findings could explain some of the different results from autopsy and from clinical follow-up studies, concerning the risk associated with different ulcer diseases. In autopsy studies such as those performed by Kühlmayer & Rokitansky, Stalsberg & Taksdal and Hilbe no evidence was found indicating a higher risk for gastric ulcer patients. On the other hand, several clinical follow-up studies performed in the time interval 20-30 years after surgery show the expected results of the gastric ulcer disease to be more frequently associated with gastric cancer death (56, 107).

If stump cancer, like cancer in the non-operated stomach is a disease related to age, the finding that gastric ulcer patients have a shorter time interval to death in gastric cancer could partly be explained. These patients were on the average seven years older than duodenal ulcer patients at surgery⁹. However, survival curves seem to be displaced 15 years. In addition, Mitschke has reported that chronic atrophic gastritis developed more rapidly and was more pronounced around the anastomosis after a resection for gastric ulcer than for duodenal ulcer. Chronic atrophic gastritis is considered to be a precancerous lesion (VII, 97). The interval to the development of cancer could then be expected to be shorter in gastric ulcer patients. In our series it was not possible to study gastric ulcer patients operated on at different ages separately. However, the relatively few patients operated on for gastric ulcer in the fourth and fifth decades of life must be regarded as having a markedly increased risk of developing cancer.

The risk of dying from gastric cancer increases exponentially with time after surgery.

The interval between primary operation and diagnosis or death in gastric cancer has been commented on in every report on gastric stump cancer. Hellers et al, in an epidemiological study analysed the incidence of gastric cancer in Stockholm county in the general population as well as among those resected for benign gastroduodenal disease more than 15 years earlier. They estimated the population at risk to be 10 235. During three years 87 stump cancers were diagnosed. The incidence increased with time after surgery. In our series we found an exponentially increased risk of dying during successive five-year intervals. We have recalculated and plotted the reported incidence data of Hellers et al and our own mortality data (II) in the

same figure (Fig 1) and a striking similarity was found. Incidence rate and mortality rate could be compared to gastric stump cancer as the prognosis after diagnosis was miserable during the major period in which our series was collected.

Our data estimate the risk of dying from gastric cancer during a specific five-year interval. For duodenal ulcer patients in an interval 10-20 years after surgery the risk is probably somewhat less, as compared to the estimation based on all patients.

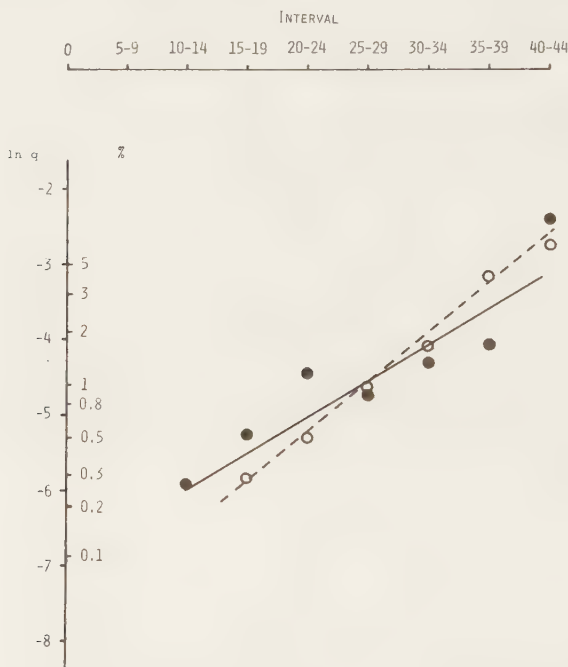


Fig 1. Risk of dying (q) from gastric cancer during successive 5-year intervals after surgery. Filled dots (●) denote data from II. Open dots (○) denote data from Hellers' et al (55).

Patients operated on before the age of 40 run a four-fold increased risk of dying from gastric cancer.

The importance of age at surgery as a risk factor has earlier been described by Brollo et al in an autopsy study. They found that the relative age specific risk of dying in gastric cancer was 2.5 in patients operated before the age of 45 and 0.6 in patients operated above that age. Our data show decreasing relative risk with increasing age at surgery, while an increasing relative risk was expected. The age at which the expected and the observed risks were equal, was calculated to 51 years. We consider this partly a consequence of the previous finding of an increased risk with increasing time interval after surgery. A patient operated on at 35 years of age has reached 55 at 20 years after surgery when the risk of dying of gastric cancer starts to be notable. At 55 the risk of succumbing to other diseases is low. If low age at surgery as such is a risk factor besides being a prerequisite for a long observation time is open for discussion.

The information could be used in the clinical situation when considering a gastric resection. If the patient is above the age of 50 a resection may contribute to a decreased relative risk of dying from gastric cancer. On the other hand, if the patient is below 40 years of age, another surgical procedure should be considered, e.g. selective proximal vagotomy for duodenal ulcer and possibly resection with Roux-en-Y reconstruction for gastric ulcer patients. However, there are no clinical data available suggesting that these operations are accompanied by a lesser risk of developing cancer during long-term follow-up. We have to rely on experimental data suggesting that these procedures are associated with the least risk (82).

We have identified some risk factors in patients operated on for benign gastroduodenal disease and suggested how to use the information in the clinical situation. The findings can naturally not be used to exclude the possibility of a gastric stump cancer in an individual patient. Furthermore, none of the findings prove that surgery per se causes gastric stump cancer. Criteria for surgery during the period studied may coincide with Nature's own selection of high risk patients.

From 1970 to 1980, 39 patients with advanced gastric cancer and 22 with early cancer were diagnosed and treated at the Department of Surgery in Lund. During the period the series was collected gastroscopy and biopsy was the main diagnostic procedure to examine patients operated on for benign gastroduodenal disease and complaining of upper gastrointestinal symptoms. Fifteen early and six advanced

cancers were diagnosed among patients offered screening to detect cancer at an early stage. Patients with early cancer were, if possible, subjected to re-resection. A total gastrectomy and lymph node dissection around the coeliac axis and its branches was the procedure of choice aiming at the curative treatment for patients with advanced cancer.

The latent period for advanced gastric cancer decreases with increasing age at primary surgery.

This finding confirms earlier reports on the relation between age at surgery and length of the interval to diagnosis of advanced cancer. The regression line fitting our observations had the same regression coefficient as that reported by Schmidt et al from West Germany. One interesting feature with gastric stump cancer is the difference in numbers detected in different geographical areas. Most reports on this subject come from Europe. In the United States the incidence of gastric cancer in the general population is low and in Japan high. From both countries reports on cancer in the gastric remnant are rare (36, 57). Does the latent period differ in different geographic areas? Dougherty reports a clinical material from Minneapolis where the average interval between surgery and the diagnosis of advanced stump cancer for patients less than 50 years of age at surgery was 31.5 years. In this series the corresponding figure was 26 years indicating that latent periods may differ in different geographic areas. If so, it will be shown when the same equation is calculated on the basis of a clinical material collected in a low risk area.

We have previously shown that patients with duodenal ulcer develop cancer after a longer interval than those with gastric ulcer. As most young patients are operated on because of duodenal ulcer and elderly patients for gastric ulcer the relation between age at surgery and latent period could to some extent be expected.

The mean latent period for early gastric cancer is 23 years and not correlated to age at primary surgery.

In several reports the occurrence of early gastric cancer (EGC) in the resected stomach has been described (III). The mean latent period for

12 patients collected from four different series (32, 33, 114, 125) is 22 years (range 13-33) and similar to our findings of 23 years in 21 Billroth-resected cases. Among patients with AGC a relation was found between age at surgery and length of free interval. Such a relation was not apparent in patients with EGC. However, when plotting age at surgery to age at diagnosis the correlation coefficient was 0.81 and the regression coefficient 0.82, indicating that EGC is characterized by uniform latent period regardless of age.

In patients operated on after the age of 50 few cases of EGC have been reported. The collected data indicate, however, that EGC:s, also in this age group are diagnosed 20 years after surgery. The length of the free interval for AGC is usually shorter than 20 years in these patients. If these findings seem incompatible they could be explained by the following hypothesis:

There are two different types of gastric cancer in the resected stomach, one dependent on the operation and one independent of the initial surgical procedure. The incidence of the independent cancer is decreased to one half or one third by the resection, but otherwise parallels the age dependent incidence rate of gastric cancer in the general population. The dependent cancer has an induction time to EGC stage of 23 years and the length of induction time is only influenced by the type of ulcer disease, e.g. somewhat shorter in gastric ulcer and longer in duodenal ulcer patients. At a young age the majority of patients are operated on for duodenal ulcer. The proportion of gastric ulcer increases gradually with age at surgery but not until the seventh decade of life are as many duodenal as gastric ulcers operated (I). The mean interval for EGC should then only slowly decrease in length, with increasing age at surgery in a clinical series. When operated on above the age of 50, patients will be in their seventies before the dependent EGC occurs. At that time death from other causes is more common which could explain why EGC is then diagnosed in decreasing numbers. Earlier we calculated the risk of dying of gastric cancer when operated on above the age of 60 to be approximately one half of the expected. These cancers should, according to the hypothesis, be of the independent type as only a few patients operated on at an age above 60 will survive 20 years. In that case the age at diagnosis should correspond to that for gastric cancer in the general population, where most cancers appear in the seventh decade of life, explaining the short interval between gastric surgery for a benign gastroduodenal disease and the occurrence of stump cancer.

The typical EGC is of the intestinal type (III). Even if it is tempting to suggest that the intestinal type is the typical dependent cancer, related to the anastomosis where bile reflux causes the precancerous lesion, chronic atrophic gastritis, intestinal metaplasia and atypia, several objections could be raised. For a critical analysis of the histogenetic aspect of intestinal and diffuse type of EGC in relation to atrophic gastritis and intestinal metaplasia the reader is referred to the work of Johansen. In his series at least 10

out of 27 EGC of the diffuse type, chronic atrophic gastritis and intestinal metaplasia had contributed to their development. In advanced cancer the ratio between intestinal type and diffuse type is approximately the same in the operated as in the non-operated stomachs (57, 137). One probable explanation as to why EGC of the diffuse type is so rarely diagnosed is that they are usually not accompanied by a typical endoscopic picture.

Further work on the localization and cancer type in relation to age at surgery and length of free interval may yield data to support the hypothesis.

The yield of a screening procedure can be increased.

In II we found the relative risk of succumbing to gastric cancer to be related to the age at primary surgery. Patients operated on before the age of 51 ran an increased risk compared to the general population. Screening should be reserved for patients with an increased risk. As patients operated on above the age of 50 are excluded, the total number of patients to be examined is reduced by at least one third. The mortality rate increases exponentially with time after surgery. Consequently, to get a high yield of gastric cancer it is important to start as late as possible after the operation. Patients operated before the age of 50 developed an EGC after approximately 23 years and AGC after a mean interval of 26 years. Earlier recommendations to start screening 15 years after surgery seem to imply too short a period to yield a sufficient proportion of cancers. A starting point for screening should take into account patient's age at surgery and the length of the free interval. In Figure 2 both AGC and EGC in the clinical series described in III were plotted (cancers after gastroenterostomy excluded). The regression lines were calculated separately. A line is drawn representing a theoretical starting point in relation to age at surgery and length of free interval. As seen in Figure 2, 21 out of 25 advanced and 17 out of 21 EGC diagnosed in Lund appeared after a longer latent period.

Thus in patients resected at 30, 40 or 50 years of age it is time to start screening when they reach the age of 51, 60 and 68 years, respectively.

Free
interval

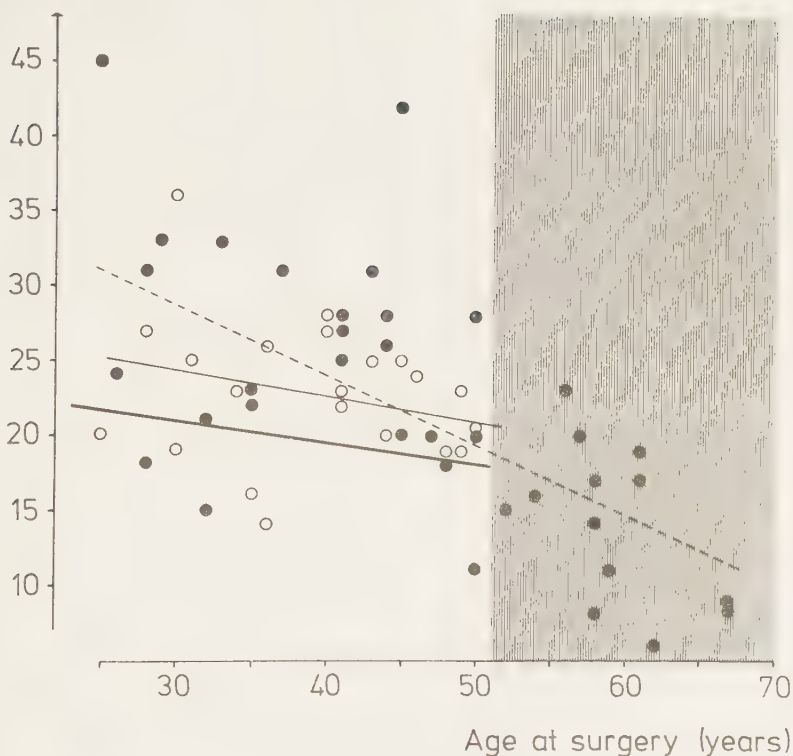


Fig 2. Patients with gastric stump cancer. Age at surgery and length of free interval for Billroth-resected patients in III. Filled dots (●) denote AGC and open dots (○) EGC, (---) regression line for AGC and (—) for EGC. (—) indicates the theoretical time for initiating screening. Patients operated above the age of 51 (shadowed area) should not be screened.

Endoscopic resources are limited in most medical centres. Screening could be generally recommended if a limited number of patients are to be examined. It is possible to calculate the amount of extra work for one endoscopy unit with the above recommendations. Hellers et al estimated the number of patients who more than 15 years earlier were resected for benign gastroduodenal disease in Stockholm county to be 10 235. We can exclude 1 734 patients who were resected between 15 and

20 years earlier. Further 868 patients who were more than 80 years old could be eliminated from screening. Presumably at least one third were operated on after the age of 50 leaving approximately 5 100 patients with an increased risk of developing gastric stump cancer where screening could be considered. If the number of initial screening examinations is spread out during a three-year period and the average interval to a re-examination calculated to three years, the number of examinations to be performed per year is reduced to 1 700. With a participation rate of 60 % and the patients divided into six different endoscopy units in Stockholm 180 examinations per centre per year have to be performed. Thus if each centre has the capacity to perform one extra gastroscopy four days a week resources are available for performing screening among operated patients selected on the basis of the above mentioned theoretical criteria. It does not seem impossible to organize such an activity and the costs of detecting one gastric cancer at an early stage could be expected to be reasonable.

Proof of screening efficiency in terms of reduced mortality in gastric cancer is hard to detect.

The effect of the introduction of a new diagnostic technique, able to diagnose cancer at an early stage on the cancer mortality rate, has been discussed for carcinoma of the breast and cervix (80, 81, 128). When the diagnostic technique is used for screening without control groups the effect on mortality rates are difficult to interpret (88). In Japan screening for gastric cancer in the general population has been routinely used beginning 15 years ago. The ratio of EGC to AGC has reached 1:2-3 in many centres (38). The gastric cancer mortality rate has decreased (135). To what extent this is due to the many EGC detected, the diagnosis of AGC at a curable stage, more effective surgical techniques, adjuvant chemotherapy or a spontaneous decrease in cancer mortality in the population has not been thoroughly investigated.

When initiating a screening program for gastric cancer with gastroscopy and biopsy among operated patients in 1972/1973 45 % of the patients participated. A similar distribution of risk factors were found among patients that did not participate. These have thus been used as controls and our intention is to continue regular screening of the initially examined patients and to follow the controls.

After seven years no difference in cancer mortality rates between the two groups is apparent despite the fact that 15 EGC were operated among screened and only two among not screened patients. Mortality rates in both groups were twice the expected from the age and sex

matched general population. The groups are small in numbers and a selection of symptomatic patients with AGC to the initial screening, cannot be ruled out. A longer follow-up is probably necessary to detect possible differences.

From experience gathered during the first five years of follow-up we calculated the incidence of EGC in relation to length of interval between primary surgery and diagnosis. The five year incidence of EGC was five to ten times higher than AGC mortality rates in corresponding intervals. The question then arises if it is probable that all EGC proceed into AGC. If incidence figures are valid also for the control group there ought to be 10-12 patients with EGC among the control patients in 1979. The interval from primary surgery was then an average of 28 years. The risk of dying from gastric cancer during the next five years has earlier been calculated to be approximately 1.5 % (II), e.g. we could expect five patients to succumb to gastric cancer during the following five years. It thus seems unlikely that all the 10-12 EGC:s thought to exist among control patients proceed into an advanced stage. Patients are old but it is not likely that half of the patients will die from unrelated causes during the following five years. Some EGC:s will probably remain in the early stage. This is not an unreasonable assumption since in many cases of EGC in the non-operated stomach the time for the tumor to double its superficial extension has been shown to be 1-3 years (21).

Patients judged suitable for surgical intervention because of an EGC pose a minor therapeutical problem. In elderly high risk patients we are in urgent need of information in order to predict the invasive tendency of EGC. Meanwhile we are not convinced that an elderly high risk patient, with an intestinal type of EGC restricted to the mucosa should be recommended a re-resection. Rösch & Frühmorgen has used Argon lazer to treat precancerous lesions. It will be interesting also to test this type of treatment in selected EGC patients.

A re-resection is recommended as the surgical treatment of early gastric cancer in the operated stomach.

EGC is most often found adjacent to the anastomosis in an operated stomach (53). As it is often multifocal and the extension sometimes difficult to establish total gastrectomy has been recommended as the surgical treatment (125). We agree completely with the statement that after re-resection the possibility exists of leaving areas of EGC behind. However, postoperative complications are much more common after total gastrectomy than after a re-resection. The majority of patients are old when an EGC is diagnosed. With repeated careful pre-

operative gastroscopic and bioptic examinations of the gastric remnant it has been possible in most cases to establish the extension of the superficial early cancer. A focus of early cancer was probably left behind in only two out of 22 cases and these became apparent within two years after surgery (III). Both were then subjected to total gastrectomy and are alive four and two years postoperatively without signs of cancer. Longer follow-up is, however, necessary to establish the true recurrence rate after re-resection.

Naturally, if a part of the gastric remnant is left behind, follow-up with gastroscopy and biopsy is necessary. The difference in mortality rate between total gastrectomy and re-resection is of such a magnitude that a two-stage procedure in 10 % of the patients can be accepted.

Five-year survival rate after surgical treatment for advanced cancer in the operated stomach is similar to that of gastric cancer in the general population.

In a survey of literature Pietsch & Burkhardt found that 43 % of 1 659 patients had been subjected to a curative and 4 % to a palliative resection. Half of the patients were either not operated or had only an exploratory laparotomy. Thirty-three patients or 4 % of the resected cases survived five years. These findings are strikingly different to our experience. We found a curative resectability of 55 %, and a palliative resectability of 18 % with a five-year survival rate among resected patients of 30 %. According to our data 55 % of the patients with a tumor restricted to the gastric wall without penetration of the serosa, with or without lymph node metastases in the immediate vicinity of the tumor survived five years. The figure is based, however, on a small number of patients. The standard deviation of the five-year survival rate was 20 % indicating that with 95 % confidence limit the five-year survival rate is at least 15 % in this stage of the disease. If the 33 survivors in Pietsch & Burkhardt's collected series were selected from a group of patients in a similar stage, the group could at most consist of 220 patients. The difference between 220 out of 1 659 is significantly less than 11 out of 39 ($p < 0.05$), suggesting that early diagnosis probably has contributed to more long-term survivors in our series. When the tumor had grown through the serosal layer or spread outside the regional lymph nodes the chance of surviving five years was only 9 %. We had no indications that the six patients subjected to palliative total gastrectomy benefitted from the operation. However, one patient survived 7.5 and another 2 years postoperatively. In all cases the procedure was performed because of obstruction or bleeding and in these respects all patients were palliated.

In most series the postoperative mortality rate varies between 20 to 50 % indicating a late diagnosis with surgery performed on cachectic patients (105, 108, 148). Radomsky et al report a mean delay of 10 months before the correct diagnosis could be established. The mean length of AGC symptoms prior to the diagnosis was five months in our series and the postoperative mortality 8.5 %. This again suggests that early diagnosis may contribute to a better prognosis for patients with AGC of the operated stomach.

Comparing five-year survival from cancer in the resected stomach with that in the intact stomach is not quite fair as total gastrectomy in most cases is necessary to treat stump cancer. Still, Inberg et al reports a five-year survival rate in 2 590 gastric cancer patients to be 26 % after curative and 3 % after palliative surgery. These figures are comparable to what we have found in our clinical series of advanced cancer of the gastric remnant.

A series of 357 patients operated on for benign gastroduodenal disease 12-42 years previously were screened for gastric cancer with gastroscopy and biopsy in 1972/1973. When questioned 31 % of the patients reported one or several symptoms referable to the upper gastrointestinal tract. Gastroscopy was performed by one endoscopist who classified the degree of endoscopic reflux gastritis (ERG) in arbitrary units. In 1978/1979, 175 patients of the original series underwent a second gastroscopic screening by another endoscopist who tried to evaluate and separately classify the individual gastroscopic characteristics of ERG. At both occasions biopsies were taken. These were examined by one pathologist, without knowledge of endoscopical findings. The degree of histological changes such as acute gastritis (AG), chronic gastritis without atrophy (CG), chronic gastritis with atrophy (CAG), chronic hyperplastic gastritis (CHG), intestinal metaplasia (IM), and atypia (API) was classified and expressed in arbitrary units. Correlations between symptoms, endoscopic and histological findings were studied.

The syndrome of postoperative reflux gastritis can be regarded as a clinical entity with good agreement between the symptoms of postprandial fullness, nausea, pain and bile-stained vomits and the severity of endoscopic reflux gastritis.

Postoperative bile vomits were early recognized as a complication in gastric surgery. The etiology was considered to be an intermittent mechanical obstruction, and the term afferent loop syndrome was adopted (26). As a consequence patients with disabling bile vomits were reoperated with an enteroanastomosis between the afferent and efferent loops or converted from Billroth II- to Billroth I-anastomosis. However, in many patients postprandial vomiting was not discontinued (2). At the end of the sixties, simultaneously with the dawn of modern gastroscopy era, the syndrome of postoperative reflux gastritis (PRG) was adopted after clinical studies of Wells & Welbourn and van Heerden and others. Experience from gastroscopy in symptomatic patients showing an ample reflux of bile and severe hyperemia around the anastomosis, fitted well with experimental works on the injurious effects of bile on the gastric mucosa (7, 29, 30, 84). The concept of PRG was adopted with enthusiasm also at the Department of Surgery in Lund. Favourable results after Roux-en-Y conversion in symptomatic patients were reported (12, 13, 49, 58, 65, 127). Criteria for the diagnosis of PRG were suggested by van Heerden et al as being pain, bile vomits, anaemia, gastric hyposecretion and endoscopic evidence of gastritis. However, not all bile diversion operations proved successful even if patients preoperatively fulfilled the criteria for the syndrome of PRG (1, 72). The reason for failures were many. Most resected patients have evidence of endoscopic reflux gastritis (ERG), hyposecretion and anaemia. Pain could be caused by other conditions such as biliary and pancreatic diseases, oesophagitis and the irritable bowel syndrome. Pain could per se provoke epigastric fullness, nausea and vomiting. The need for discriminating diagnostic tests is obvious.

We want to stress that gastroscopy and routine biopsy have not been proved to be a diagnostic test for the identification of the concept of PRG. Most patients with severe ERG have no symptoms and at least half of the patients with symptoms have fairly normal findings (V). Our study has shown that a group of patients with certain symptoms has more pronounced endoscopic and histological changes than patients lacking those symptoms. This indicates that the causative factor has the possibility of provoking symptoms as well as histological changes and a gastroscopic picture of severe ERG. The important question of the relation between the etiological factor(s) and a symptom or combination of symptoms has not been analysed. The term PRG indicates a simple relation between the reflux of duodenal contents into the operated stomach and specific symptoms, but this is obviously false. Furthermore, a severely altered gastric mucosa does not seem to be a necessary condition for the causative factor to provoke symptoms.

The symptoms best correlated with severe histological and gastroscopic changes are postprandial fullness and bile vomits. If the concept of PRG should be based on a combination of symptoms and severe gastroscopic and histological findings these two symptoms ought to be included. There is general agreement that bile vomits should. The symptom postprandial pain correlated less well with the degree of ERG and not at all with the degree of histological changes. The statement that pain should be included in the concept of PRG is based mainly on the experience from patients with disabling symptoms in surgical series. Among such patients pain may well dominate the reported symptomatology. Even if the patients actually experienced epigastric fullness the symptom was perhaps not noted. It can, however, not be ruled out that some of the failures after surgical treatment are due to the selection of patients with epigastric postprandial pain as the dominating symptom. Further studies must show that the causative factor has the properties of provoking pain in some patients without micro- or macroscopic changes. Meanwhile, other possible etiologies to pain must be ruled out before accepting it as a part of the syndrome of PRG.

Endoscopy is recommended as the first diagnostic procedure in patients complaining of postgastrectomy symptoms (V). In patients with bile-stained vomits indications for gastroscopy could be wide since it is the symptom best selecting patients with early gastric cancer. In an individual patient the etiology of symptoms can be established if oesophagitis, advanced gastric cancer or recurrent ulcer is found. Biopsies may give further information when severe ERG, polyps or erosions are detected. However, the diagnosis of PRG could not be confirmed by an endoscopic and histological examination. In clinical practice we have to rely on a thorough penetration of the quality and quantity of symptoms and rule out other possible etiological factors, and hope that future standardized provocation tests will be able to establish diagnostic criteria for the concept of the syndrome of reflux gastritis (1, 45, 61, 62, 109).

When judging the degree of endoscopic reflux gastritis special attention should be paid to the occurrence of yellowish zones in the anastomosis and bile admixture to the gastric secretion.

Endoscopic findings in the resected stomach have been described in terms of hyperemia, congestion, erosions, thin and easy bleeding mucosa (37, 71, 127, 145). Lipid islands are often seen (34, 139). Janunger & Domellöf have reported the frequency of polyps in the operated stomach to be 9 % and sometimes the only sign of an EGC. Several investigators have not been able to establish a correlation

between the degree of endoscopic and histological findings. In reports on the result of screening examinations endoscopic findings are defectively reported while histological findings in biopsies are described in detail, although the typical endoscopic picture is well known to all experienced endoscopists.

Before the first screening procedure in 1972/1973 BH defined four grades of ERG. Special attention was paid to three easily recognizable and gradable findings, e.g. redness of the mucosa, yellowish zones in the anastomosis and reflux of bile during the examination. The first analysis of data showed that yellowish zones were an important sign of severe histological changes as a positive correlation was found between the degree of ERG and the degree of CAG, CHG, IM and API. During the second screening data were collected in order to evaluate individual gastroscopic signs in relation to histological findings in biopsies, with the assumption that some were more important for evaluating probable precancerous lesions. The analysis showed an anticipated good and positive correlation between the occurrence of yellowish zones and degree of CAG, IM and API. We also expected to find a correlation with the intensity of reddening around the anastomosis, as that sign is reported to be typical for ERG. In 142 examinations we could only find a correlation with the degree of CAG and API at the 5 % level. Earlier failures to find an association between endoscopic and histological data may be explained by the fact that too much attention has been paid to the reddening of the mucosa around the anastomosis. Furthermore, as to our definition (V) in the most severe degree of ERG, the gastric mucosa looks thin, rigid and fragile. The typical reddening around the anastomosis is then not dominating the endoscopic picture any longer.

It was surprising, however, to find that such a simple observation as the degree of bile admixture to the gastric secretion correlated to the degree of CAG, CHG, IM and API in biopsies taken around the anastomosis. If the observation represents the degree of bile admixture in the fasting stage, the agent(s) causing the histological changes probably follows the bile. Furthermore, the degree of invagination of the afferent loop into the gastric remnant (regarded by us as one anatomical prerequisite for bile reflux) was also associated with severe microscopical changes. It is tempting to speculate on the invagination causing a valve mechanism where postprandially the duodenal contents empty easily into the stomach whereas the gastric contents simultaneously have difficulties in entering the afferent loop, causing epigastric fullness and later bile-stained vomits. Alexander-Williams (1) radiological studies on patients with severe symptoms after Billroth II-resection may indicate that such a mechanism could actually be valid. He observed that duodenal content emptied into the gastric remnant. The mixture of bile, food and radiopaque contrast medium in the stomach emptied only with difficulties through the afferent loop. Regrettably we did not register individual symptoms at the second screening to be able to correlate these to the degree of invagination. Further studies have to

be performed to find out if invagination of the afferent loop into the gastric remnant is a discriminating sign of the syndrome of postoperative reflux gastritis.

It must be pointed out that the correlation between endoscopic and histological findings is only applicable to a Billroth-resected stomach. After Roux-en-Y reconstruction a correlation could not be detected in 58 patients despite the fact that histological changes in biopsies were as common as after a Billroth-resection (43).

Suggested criteria for biopsy in the operated stomach are tumor, ulceration, erosion, polyp and pronounced endoscopic reflux gastritis.

With modern fiberoptic instruments the resected stomach is easy to examine. Problems may occur if a gastroscope with prograde optics is used to examine and take biopsies from the minor side of the anastomosis in a Billroth I-resected stomach. A change to a side-viewing instrument is then recommended. Biopsies should always be taken from tumors. We have not experienced any benign tumors above 2 cm in diameter. Polyps in the resected stomachs are commonly found. During the first screening 13 patients with one or several polyps near the anastomosis were detected giving an incidence of 4 %. One patient had an EGC surrounding the polyp. We agree with Janunger & Domellöf that the presence of a polyp indicates that multiple biopsies should be taken and the polyp extirpated with a polypectomy snare for further histological examination.

We have never seen a benign ulceration surrounded by gastric mucosa in the resected stomach except surrounding retained sutures. An ulceration should always be regarded as an ulcerating carcinoma. Benign ulcerations are almost exclusively situated on the intestinal side of the anastomosis. Ulcerations in the anastomosis may be malignant and must therefore be followed with multiple biopsies until completely healed.

Gastric mucosal erosions adjacent to the anastomosis may be a sign of EGC and biopsy is recommended. The incidence of anastomotic superficial erosions was 8 % in the second screening series but biopsies showed no signs of cancer.

The majority of patients have varying degrees of ERG without other pathological findings. Routine biopsy has been recommended irrespective of endoscopic findings, justified by the statement that EGC in the operated stomach is not always possible to detect gastroscopically (33, 125). However, many experienced endoscopists do

not follow these recommendations but take biopsies only when severe changes are seen. Do they miss relevant findings? In our experience they do not. A prerequisite for such a statement is that the endoscopist is experienced and knows how to interpret the findings. If attention is paid to the occurrence of yellowish zones in the anastomosis, pronounced reddening of the mucosa around the anastomosis and bile admixture to the gastric secretion and the "burned out lesion", the thin, rigid and fragile mucosa very few relevant findings are missed if biopsy is omitted. If selection criteria for biopsy was the above during the two screening procedures all cancers except one EGC had been diagnosed. This EGC was a small diffuse type of cancer (according to the Laurén classification) accompanied by only discrete ERG. As 50 % of advanced and only 14 % of early cancers detected during the seventies at our endoscopic unit were of the diffuse type we have probably missed more EGC of the diffuse type despite routine biopsy. In our opinion it is not reasonable to increase the cost of an examination with approximately 50 % with such a poor yield (5). Furthermore a large number of routine biopsies may fatigue the pathologist to the extent that he becomes less observant on discrete but relevant findings, which may contribute to an opposite effect on the number of EGC:s detected.

On the basis of clinical data, endoscopic and histological findings, an individual follow-up schedule for a patient can be established.

Earlier we have described the risk of developing cancer on the basis of clinical data such as age at surgery, length of free interval and type of ulcer disease. After an examination because of symptoms or as a screening procedure the patient wants a prognosis, e.g. after how long an interval could a re-examination be recommended and what is the risk of developing gastric cancer in the future?

Stockeland et al followed up 59 out of the initial 108 screened patients after three years. The histological changes were found to be stable and no new cancers were detected. They recommended a follow-up interval of 3-5 years. The size of the follow-up interval is in accordance to our opinion, but could recommendations be given more in detail?

In VI we stated that biopsy was indicated only if ERG was pronounced (ERG 3-4) and in IV that EGC probably could remain in the early stage for some years. Table I in VII shows that two advanced gastric cancers appeared during follow-up among patients that lacked or had moderate ERG where no biopsies are recommended. These two AGC:s were both found in the second screening six years after the first examination. Out of

the five EGC:s one was detected at the second screening and two during examination because of symptoms. Two patients had been scheduled for regular follow-up. One of these insisted of being examined each year and the other had severe histological changes in biopsies. In both cases an EGC was diagnosed after three years. Thus, in one patient the interpretation of the microscopic findings in biopsies changed the length of the follow-up. If endoscopic findings are discrete and the patient belongs to a group with moderately increased risk as judged from clinical data, five-year intervals between examinations seem to be sufficient. In high risk patients, such as patients operated more than 20 years ago for gastric ulcer at an age less than 40 the interval could be shortened to three years. In patients with pronounced ERG additional information could be given by the pathologist. In VII we showed that increasing degrees of CAG, CHG, IM and API were associated with an increased risk of developing cancer. High degrees of CHG are less suitable as an indicator of risks involved as it is commonly found in biopsies. Severe CAG and IM and the degree of API could constitute a basis for a histological judgement of risks.

Further analysis may yield data on the combined effect of different histological parameters concerning the risk of developing gastric cancer.

Meanwhile, endoscopists and clinical pathologists must exchange experience in regular local meetings so that routines can be established on the basis of both specialists' knowledge in this field. Statements based on statistical information implies a risk of making mistakes, but if calculations are based on significant data most patients will benefit. The work of Ohlert et al (121) on cariometric and histochemical tests showing that the individual malignant potency of certain histological changes can not be established. This type of reports may contribute to the pathologists' disinclination to express an opinion on the prognosis in the individual case. A coding system expressing the risks involved ought to suit both the clinician and the pathologist. Biopsies from patients could for example be classified in mild, moderate and severe changes suggesting an interval between examinations to be 3, 2 and 1 year, respectively. The clinician then carries the responsibility of putting forth a suggestion to the patient about future management based on the evaluation of risks involved judged from clinical, endoscopic and histological data.

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